THE ASSOCIATION OF PATIENTS' ANALGESIC TREATMENT BELIEFS AND TRADE-OFFS WITH ANALGESIC ADHERENCE BEHAVIORS AMONG OUTPATIENTS WITH CANCER PAIN

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DEDICATION

For the patients, families, and communities I have been so privileged to care for

and

for my palliative care colleagues working to alleviate

serious health-related suffering worldwide.

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Words fall short in expressing the overwhelming extent of gratitude I have for the inspirational, expert faculty at the University of Pennsylvania, scholarly mentors, clinical and academic colleagues, professional organizations, my spiritual and healing communities and - my very foundation of love and support – my incredible friends and family. I am a blessed and fortunate man.

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I guess when you're grateful – you're just really grateful.

From my heart… thank you.

ABSTRACT

THE ASSOCIATION OF PATIENTS' ANALGESIC TREATMENT BELIEFS AND TRADE-OFFS WITH ANALGESIC ADHERENCE BEHAVIORS AMONG OUTPATIENTS WITH CANCER PAIN

William E. Rosa

Salimah H. Meghani

Pain is one of the most burdensome symptoms for patients with cancer. Per cancer pain guidelines, opioids remain one of the primary modalities for managing moderate to severe cancer pain. Analgesic nonadherence is common among cancer patients despite unmanaged pain symptoms. We investigated how patients prioritized analgesic treatment beliefs for cancer pain and whether those beliefs predicted objective analgesic adherence behaviors.

This is a secondary analysis of an existing dataset (n=207) that used a three-month prospective observational design. Subjects were from outpatient oncology clinics of a large Philadelphia health system and were $\geq$ 18 years, self-identified as African-American or White, diagnosed with solid tumor or multiple myeloma, and prescribed at least one around-the-clock analgesic for reported cancer pain.

We conducted three studies to achieve the aims. First, we performed a concept analysis (Chapter 2) of analgesic nonadherence for cancer pain and qualified its utility in the context of the United States opioid epidemic. In Chapter 3, we used maximum difference scaling to identify how patients traded-off on analgesic treatment beliefs. Utilities (importance scores) were ranked using a *k* means cluster analysis; clusters were

compared in terms of key variables. Finally, we employed general linear modeling to evaluate if analgesic belief clusters predicted analgesic adherence behaviors, assessed longitudinally using electronic medication monitoring while accounting for relevant confounders (Chapter 4).

Initial results showed beliefs weigh significantly in subjective analgesic trade-offs. We identified two distinct belief clusters. Side effect severity was the only variable that significantly differed between clusters. Subjects mostly traded-off based on the belief, 'pain medicines keep you from knowing what is going on in your body.' Addiction was not a top priority. Belief clusters did not predict analgesic adherence. However, in an adjusted analysis, it was the experiential variables (e.g., side effects, most potent analgesia, pain relief with analgesics, duration of disease), as well as patients' race, that were statistically significant in explaining analgesic adherence.

Our findings suggest that experiential variables rather than analgesic beliefs were associated with analgesic adherence in this sample of cancer outpatients. Additional studies should explore patients' cancer pain self-management practices while considering patient, provider, and system/ structural factors to optimizing cancer pain management.

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CHAPTER 1

Introduction

Introduction

Pain has been identified as one of the most common experiences of the cancer trajectory (Shi et al., 2011). A recent systematic review and meta-analysis of 112 studies on pain (n=63,533) and pain severity (n=32,261) suggests an estimated two-thirds of patients with advanced or metastatic cancer report some pain, and up to 38% of patients report their pain as "moderate" or "severe" (van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016). Many patients with moderate to severe cancer pain require complex analgesic regimens, at times including a combination of nonopioids, short- and long-acting opioids, and adjuvant prescriptions to effectively mitigate pain and achieve an acceptable level of function and quality of life (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; World Health Organization [WHO], 1986, 1996, 2018). Unfortunately, there is limited empirical cancer pain data available. The chronic pain literature often excludes patients with cancer from the very studies that inform pain management guidelines, drive policies, and establish prescribing standards for analgesics, including opioids (Meghani & Vapiwala, 2018).

Among the many challenges identified in managing cancer pain is patient deviation from prescribed analgesic regimens. This concept is known as "nonadherence". Nonadherence to analgesics may complicate treatment plans and exacerbate symptoms among a population negatively impacted by cancer pain. Despite the prevalence of cancer pain, analgesic nonadherence persists and is poorly understood. A list of key terms relevant to the phenomenon of analgesic nonadherence and related concepts can be found in Table 1.

Analgesic nonadherence behaviors have a number of predictive and covarying factors. They may be influenced by an individual's beliefs, preferences, and values (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002; Jacobsen et al., 2014; Liang et al., 2013; Meghani & Knafl, 2017; Valeberg, Miaskowski, Paul, & Rustoen, 2016; Ward et al., 1993); patient and family caregiver hesitancy to use or support the use of analgesics (Lee et al., 2015; Valeberg et al., 2016); and sociodemographic considerations, such as race, socioeconomic status, and structural barriers, including insurance coverage (Bryan, De La Rosa, Hill, Amadio, & Wieder, 2008; Meghani et al., 2014; Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Valeberg et al., 2008; Wieder, Delarosa, Bryan, Hill, & Amadio, 2014) Current clinical interventions to decrease nonadherence rates have not achieved their aim. For example, Oldenmenger and colleagues reviewed 28 randomized controlled trials (n=4,735), showing patient education to reduce analgesic nonadherent behaviors are heterogenous and subpar at best, leading to a significant pain improvement outcome in less than 20% of all cancer pain patients (Oldenmenger et al., 2018). Additional studies are required to better inform tailored intervention strategies to individual and family needs in order to more thoroughly understand analgesic taking behaviors to prescribed treatment regimens and associated cancer pain burdens.

Understanding Analgesic Nonadherence in the Context of the Opioid Epidemic

Although many healthcare professionals would agree there is an ethical obligation to treat pain, that duty may be obviated by stigma and policy flux inherent to the opioid epidemic in the United States. The opioid crisis and its far-reaching implications are essential to understanding analgesic nonadherence for cancer pain. The crisis has

snowballed since the late 1990s (Centers for Disease Control and Prevention [CDC], 2018; Kolodny et al., 2015) accompanied by avid disagreement regarding the future of pain assessment and ready access to opioid-related interventions. The debate over pain assessment and the priority of pain treatment using opioids is causing confusion and misunderstanding about the indication for opioids in mitigating cancer pain; impacting how patients take their analgesics and how providers prescribe them (American Pain Society Quality of Care Committee, 1995; Baker, 2017; Meghani & Vapiwala, 2018; Phillips, 2000; Rummans, Burton, & Dawson, 2018). Major leading reports recognize the complexities of managing cancer pain, the lack of longitudinal data required to fully understand the consequences of poorly managed pain, and the struggle of dual loyalties: reducing the individual burden of cancer pain while minimizing the mounting social sequelae of opioid use in America (National Academies of Sciences, 2017; National Academy of Medicine, 2017; National Institutes of Health, 2018). Given the rapidly changing landscape of opioid use in the setting of pain management, it is natural to assume that both patient and provider perceptions of opioid use will continue to evolve given ongoing policy and practice changes across settings and systems.

Purpose and Innovation

The purpose of this research is to explore the relationship between how patients prioritize their beliefs about analgesic treatment for cancer pain and their objective adherence behaviors. This purpose is achieved through a concept analysis of analgesic nonadherence for cancer pain and two research aims, discussed in greater detail in the

following sections. The anticipated findings will fill a critical gap in the literature related to how patient beliefs influence nonadherence rates.

The trade-off methodology we will use, known as maximum difference scaling or 'MaxDiff', is underutilized in the health care literature and may provide new insights regarding how patients prioritize their beliefs related to analgesic medication for cancer pain. While there has been some data reporting how patients make trade-offs related to analgesic treatment (Meghani, Chittams, Hanlon, & Curry, 2013), MaxDiff provides an innovative approach to identifying how patients trade-off on their decisions related to analgesic use. In addressing both research aims we will strive to first identify MaxDiff derived utilities (importance scores) and, second, we will determine if these utilities predict objective analgesic taking behaviors via an electronic medication monitoring system.

Implications may inform how patient deviation from prescribed analgesics is addressed in the outpatient oncology setting and ways to individualize care based on patient priorities and beliefs, thereby improving adherence and subsequent patient, safety, and health outcomes in the future. Given the sample and study focus, this research is aligned with the NIH Minority Health and Health Disparities Strategic Plan and the NIH/NINR Strategic Plan's Areas of Scientific Focus, including symptom science, self-management, and end-of-life and palliative care.

Parent Study and Sample Description

This dissertation is based a secondary analysis of existing data (NIH/NINR RC1-NR011591: PI Meghani, S.H.) The goal of the parent study was to explain racial and ethnic disparities in cancer pain outcomes, specifically to elicit trade-offs patients with cancer pain employ in making cancer pain treatment decisions and the relationship between patients' stated preferences (using Choice-based Conjoint analysis) and their adherence to scheduled analgesic treatment using the Medication Event Monitoring System (MEMS®) (Meghani, Chittams, Hanlon, & Curry, 2013; Meghani, Thompson, Chittams, Bruner, & Riegel, 2015). The parent study used a prospective observational design employing repeated measures at baseline (T1) and 3-month follow-up (T2). The parent study researchers were able to identify analgesic nonadherence as a predictor of hospitalization (Meghani & Knafl, 2016) and noted analgesic prescribing differences between African-American and White patients (Meghani et al., 2014). Parent study data was comprised of various sociodemographic, pain, and illness-related variables, and identified deviations from prescribed analgesic regimens among patients experiencing cancer pain in the outpatient oncology setting using multiple adherence measures at T1 and T2. Additionally, patients' chart data was collected for all subjects in the sample.

Patients were recruited from two outpatient medical oncology services at the Hospital of the University of Pennsylvania in Philadelphia between December 2009 and August 2011. Inclusion criteria included patients 18 years or older who self-identified as White or African-American, were diagnosed with solid tumor (e.g., lung, breast, gastrointestinal, genitourinary/reproductive) or multiple myeloma, reported cancer pain,

and had at least one around-the-clock analgesic prescription. Patients receiving pain control through a transdermal system (e.g., Duragesic patch) were excluded. Once the research assistant verified that criteria eligibility were met, the patient's oncologist verified eligibility.

A sample of 241 subjects agreed to participate, were deemed eligible, and completed baseline assessments at T1. There was a 14% attrition rate over the three-month period due to patient's death, their being too sick to complete the study, refusal to participate, or loss to follow-up. Two hundred and seven subjects completed the study at T2. The sample for this dissertation (n=207) reflects the number of subjects who completed the parent study since both cross-sectional analysis at T1 and longitudinal methods involving T2 will be employed.

Specific Aims and Respective Hypotheses

Specific Aims of this dissertation are to:

1. Clarify the concept of analgesic nonadherence for cancer pain and qualify its utility with respect to the United States opioid crisis. A conceptual definition of *analgesic nonadherence* will be identified through a rigorous synthesis of the literature for the purpose of parsimonious consistency in future use and application (Chapter 2).
2. Elicit the trade-offs patients make about analgesic treatment for cancer pain based on their analgesic beliefs and concerns (Chapter 3).
   2a. Identify and rank MaxDiff-derived patient utilities regarding analgesic beliefs and concerns.

2b. Using utilities identified in 2a., conduct *k* means cluster analysis to identify distinct cluster membership among patients based on analgesic beliefs and concerns.

2c. Describe cluster membership in 2b, by comparing key sociodemographic and clinical variables.

Hypothesis: *There will be unique subsets of cancer patients based on how they prioritize analgesic treatment beliefs for cancer pain and distinct differences between how patients prioritize their beliefs that will be decipherable among clusters.*

3. Explore whether the previously identified analgesic treatment belief clusters predict objective analgesic adherence over a three-month period as measured by an electronic medication monitoring system (MEMS®) while accounting for relevant confounders (Chapter 4).

   Hypothesis: *Cluster membership based on analgesic treatment beliefs and concerns will predict differing levels of analgesic adherence.*

Chapter Synopsis

This dissertation uses a "three-paper" format, as described below.

Chapter 1

Chapter 1 herein is an introduction and serves as an overview of analgesic adherence accompanied by relevant background information, specific aims, and descriptions of the current and parent study content. Details regarding human subjects, a

brief overview of methods, variables of interest and instrumentation, as well as the significance, innovation, strengths, and limitations, are provided.

Chapter 2

Chapter 2 addresses specific aim 1 and seeks to clarify the concept of analgesic nonadherence for cancer pain and qualify its utility in the context of the opioid crisis for patients, providers, researchers, and policy makers through an analysis of recent literature (Rosa, Riegel, Ulrich, & Meghani, 2020). Although the terms 'analgesic adherence' and 'analgesic nonadherence' are used interchangeably throughout the literature, the way the concept is operationalized in research often waivers given the study at hand. A theoretical definition will be provided for the concept that will inform consistency in use and application in the future. In addition, a conceptual model is illustrated based on the individual-, provider-, and system-level antecedents and evidence-based consequences identified during analysis. Among other conclusions discussed in more detail in Chapter 2, this author recognizes that the full impact of the role of analgesic nonadherence is yet to be determined. Figure 1 provides a conceptual model based on our analysis findings that serves as a theoretical premise for the remaining chapters.

Brief Overview of Methods and Analysis

Walker and Avant's (2019) method of concept analysis is utilized to construct a precise conceptual definition of the phenomenon for future consistency in theoretical and empirical settings. Their method consists of the following steps: 1) selecting a concept; 2) determining the aims and purpose of the analysis; 3) identifying all discoverable uses of

the concept; 4) describing the concept's defining attributes; 5) specifying antecedents and consequences; 6) articulating a model case; 7) identify related cases; and 8) defining empirical referents.

Chapter 3 Summary

Specific aim 2 is to elicit the trade-offs patients make based on their beliefs about analgesic use and rank decision-making utilities using MaxDiff scaling and cluster analysis (Rosa, Chittams, Riegel, Ulrich, & Meghani, 2019). Specific aim 2 will be achieved using MaxDiff and *k* means clustering techniques through a cross-sectional analysis of baseline sample data at T1. Outcomes include descriptive findings that identify significant differences among how groups of subjects trade-off on analgesic treatment beliefs in relation to key sociodemographic and clinical variables.

Brief Overview of Methods and Analysis

MaxDiff is a discrete choice experiment that requires subjects to identify the 'least desirable' preference related to a given attribute, as well as the 'best' or most preferred option available within a choice set (Finn & Louviere, 1992; Marley & Louviere, 2005). Thus, it is also known as "best-worst scaling" and is used to identify the maximum difference in preference between the "best" and "worst" choices available (Marley & Flynn, 2015). It boasts noted measurement advantages and distinct benefits in contrast with traditional survey techniques, conjoint analysis, and ranking methods, which may confuse study subjects with too many options in a given choice set and/or muddle findings in the absence of clear choice differences (Louviere, Flynn, & Carson,

2010; Marley & Flynn, 2015). Although MaxDiff has been traditionally used to identify consumer preferences among brands or items, the case has been made for its increased use in health care research (Flynn, Louviere, Peters, & Coast, 2007) as social sciences researchers are using it with greater frequency to better elicit patient preferences in a number of clinical settings (Feudtner et al., 2015; Louviere, Flynn, & Marley, 2015; Mooney-Doyle, Deatrick, Ulrich, Meghani, & Feudtner, 2018; October, Fisher, Feudtner, & Hinds, 2014).

Subjects in this current study were instructed to select the statement that was "most" and "least" important to him or her in thinking about their pain medications in order to calculate the maximum difference between competing priorities (Figures 2 and 3). The statements or 'attributes' provided to subjects in the parent study questionnaire were derived directly from the Barriers Questionnaire-II (Ward et al., 1993), a self-report instrument that evaluates varying aspects of how patients' beliefs function as barriers to ideal cancer pain management. The theory undergirding MaxDiff and its application to this study is described with increased rigor in Chapter 3. The ten attributes assessed using MaxDiff in the parent study questionnaire can be found in Table 2 under the "Analgesic Preference" subheading.

Once MaxDiff utilities based on analgesic treatment beliefs were identified, a cross-sectional cluster analysis of baseline data was performed to describe significant differences in preference patterns, and cluster membership was detailed in relation to key sociodemographic and clinical variables. Significant differences between the clusters

were assessed using chi-squared tests for categorical variables and analysis of variance (ANOVA) calculations for continuous variables.

Chapter 4

The goal of specific aim 3 is achieved in Chapter 4. Here, we explore whether the analgesic belief clusters identified through specific aim 2 predict objective analgesic use as measured by an electronic medication monitoring system while accounting for relevant confounders. This association was assessed based on analgesic treatment beliefs elicited at baseline (T1) and the objective analgesic adherence behaviors of patients measured at follow-up (T2).

Brief Overview of Methods and Analysis

General linear modeling using a backward elimination method will be used with the analgesic treatment belief clusters (T1) gathered in Chapter 3 functioning as an independent variable and predictor of objective analgesic adherence (T2 data). A number of clinically relevant confounders will be taken into consideration within the model, such as sociodemographic variables, level of social support, and analgesic side effects, to be discussed in depth in Chapter 4. The outcome variable in this longitudinal analysis will be objective adherence behaviors tracked with the Medication Event Monitoring System (MEMS®; Aardex, Switzerland) - a well-established measure within the analgesic adherence literature (Meghani & Knafl, 2017; Meghani et al., 2015; Oldenmenger et al., 2007; Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2017). The MEMS® is recognized as the 'Gold Standard' for measuring adherence in academic research and has

demonstrated accuracy, ease with use, and patient acceptability, showing benefits in adherence measurement over numerous limitations associated with other methods (e.g., patient report, prescription refill data, biological measurement of medicine or metabolite levels) (Butler, Peveler, Roderick, Horne, & Mason, 2004; Farmer, 1999; Parker et al., 2007; Puller, Kumar, Tindall, & Feely, 1989; Vrijens, Urquhart, & White, 2014).

Chapter 5

Chapter 5 will provide overall conclusions through an integrated discussion and synthesis of findings with implications for clinical practice, education, policy, and future research, as well as a summary of the major strengths and limitations of the dissertation.

Study Variables, Measures, and Instrumentation

Analgesic Nonadherence. The actual rate of nonadherence is poorly understood and researchers must frequently negotiate the strengths and weaknesses of available metrics (Cleemput, Kesteloot, & De Geest, 2002). There are efforts underway to stratify reporting guidelines for medication adherence, which incorporate multidisciplinary perspectives, varying patient populations, and diverse geographical areas (De Geest et al., 2018; Helmy et al., 2017). The measures of adherence in this current study include:

- *Medication Event Monitoring System (MEMS®)* is an objective metric of medication adherence through an electronic monitoring device technology (Aardex, Switzerland). MEMS® uses a microprocessor chip implanted in a medication bottle cap to record the number of times the cap is removed in real-time. This data is subsequently recorded electronically and can later be analyzed as per the given protocol. The parent

study measured around-the-clock analgesic adherence as "dose adherence", defined as the percentage of the total amount of prescribed doses taken. Methods for dose adherence calculations and a risk-reducing strategy to minimize the Hawthorne effect were published previously (Meghani et al., 2015).

Pain-related Variables. A number of pain-related variables are used to assess pain and pain treatment, medication side-effects, barriers to optimal cancer pain management, and efficacy of prescribed analgesics based on reported pain severity. Pain-related variables will be measured using:

- *Brief Pain Inventory (BPI-LF)* provides a comprehensive evaluation of pain and pain treatment variables through using a 32-item self-report instrument (Cronbach's alpha: 0.77-0.91). Of interest, we will be using pain average and pain interference scores, which are measured on an 11-point scale.
- *Medication Side-effect Checklist (MSEC)* is an 8-item scale that identifies the presence, as well as the type and severity of commonly occurring analgesic side effects (internal consistency: 0.81). Subjects are asked to rate severity of adverse effects in the preceding week on a scale of 0-10, with "0" being "no severity" and "10" being "extreme severity".
- *Barriers Questionnaire (BQ-II)* is a an 8-item revision of the original Barriers Questionnaire (Ward et al., 1993) that assesses a host of patient-reported cancer pain management barriers (subscale Cronbach's alpha: 0.75-0.85, internal consistency=0.89). Four factors establish the construct validity for the BQ-II: (1) *physiological effects* (beliefs about side effects, tolerance concerns, other

considerations about being unable to identify bodily changes in the setting of strong pain medicine use); (2) *fatalism* (fatalistic beliefs about cancer pain and respective treatment); (3) *communication* (distracting physicians from a focus on disease management through pain reporting and the equivocation of a "good" or "strong" patient with not complaining about pain); and (4) *harmful effects* (fears of pain medication addiction and their subsequent damage to the immune system).

- *Pain Management Index (PMI)* measures efficacy of a given analgesic prescription in relation to the reported degree of pain and is based on the analgesic ladder for cancer pain created by the WHO (1986, 1996). Insufficient pain management is generally reflected by a negative PMI score while an acceptably adequate analgesic prescription is indicated by a PMI score of 0 or greater. The PMI is calculated by initial identification of the analgesic "step" per the WHO cancer pain ladder (1986, 1996, 2018): step 1 = non opioid (nonsteroidal anti-inflammatory agents, acetaminophen); step 2 = weak opioid (codeine, dihydrocodeine, tramadol, combination agents [e.g., oxycodone + acetaminophen]); step 3 = strong opioid (morphine, hydromorphone, synthetic opioids, Fentanyl). Level of pain is identified per the *BPI-LF* "worst pain" rating on the previously described scale of 0-10. While more recent findings have questioned reliable implications of negative PMI scores, it continues to be a frequently used measure to evaluate adequacy of prescribed analgesic regimens in relation to patient-reported cancer pain (Deandrea, Montanari, Moja, & Apolone, 2008; Sakakibara, Higashi, Yamashita, Yoshimoto, & Matoba, 2018).

Demographic variables. The parent study questionnaire gathered information on a host of demographic variables (e.g., age, gender, self-identified race, marital status, education, computer literacy, income, health insurance, occupation, and status of employment), identified in detail in Table 2. Additional instruments related to health literacy and social support were used due to potential correlation with medication adherence, including:

- *Health Literacy Questions (HLQ)* is a 3-item scale that has performed well against the standard health literacy measure, the Test of Functional Health Literacy in Adults (TOFHLA). The HLQ was used only at T1 of the parent study to assess inadequate health literacy and asks:
    - How often do you have someone help you read hospital materials?
    - How confident are you filling out medical forms by yourself?
    - How often do you have problems learning about your medical condition because of difficulty understanding written information?
- *Sarason's Social Support Questionnaire (SSQ6)* assesses two measures of social support in a 6-item scale (e.g. availability of social support [SSQ-N] and satisfaction with available social supports [SSQ-S]). The subscales (SSQ-N and SSQ-S) measure the number of social supports and satisfaction with each of the identified supports respectively (subscale internal consistency=0.9).

Illness-related Variables. Medical chart data from each patient's record included: stage of cancer; time since cancer diagnosis; the number and types of prescribed

analgesic medications; past history of alcohol or substance abuse; presence of depression; and comorbidity score.

Table 2 provides a comprehensive list of variables to be used in the dissertation analyses, the level of data, and how they are operationalized in the data set.

Human Subjects

The parent study was approved by the University of Pennsylvania Institutional Review Board prior to its execution and all human subjects gave informed consent at that time. All protected health data was deidentified prior to commencement of this secondary analysis with no reference to personally identifiable information that may be linked to research subjects. Therefore, this work does not meet the definition of "human subjects research" according to the US Department of Health and Human Services, Title 45 CFR 46.102(f). The University of Pennsylvania deemed this dissertation study "exempt" on these grounds with no need for additional approval (correspondence on file).

Strengths and Limitations

This research maintains a number of strengths. First, a substantial advantage of this dissertation is the utilization of a rare existing dataset that allows for longitudinal and objective analyses of analgesic and opioid adherence observed in the outpatient oncology setting (Meghani et al., 2015; Meghani & Knafl, 2017). In fact, to our knowledge this is the only dataset that accomplishes these measures in the United States, with one identifiable exception of a much smaller sample size (Wright et al., 2019). Second, the sample is roughly 42% African American (African American [n=86]; White [n=121]),

representing the analgesic treatment beliefs of a traditionally underrepresented racial minority group. Findings may contribute to further advances in the field of cancer pain disparities, as well as symptom management disparities at the system level. Third, it contributes to closing the gap in better understanding the relationship between patient beliefs and objective adherence behaviors to inform improved interventions in the future. Last, as previously mentioned, it leverages MaxDiff analysis to provide the first application of the best-worst scaling method to the field of analgesic nonadherence as far as we are aware.

There are also several limitations to consider. First among these is the age of the data; collection was completed in August 2011. However, this time period occurred during the second wave of the opioid crisis (CDC, 2018) and so we contend that our findings carry relevant implications for the evolving scholarly and sociopolitical contexts related to opioids and the opioid addiction epidemic. Second, the sample is limited to self-identified African American and White patients and, therefore, it will be unable to address the potential inequities or diverse considerations related to additional racial, ethnic, or other minority groups who have been previously identified in the disparities literature (Institute of Medicine, 2003; Meghani, Byun, & Gallagher, 2012). Third, the parent study used convenience sampling to recruit from the outpatient oncology setting and does not address how beliefs inform nonadherence behaviors in the inpatient, acute, long-term, or rehabilitative settings. However, it is impossible to perform MEMS® monitoring with a probability or population-based sample and would be difficult to recruit random clinical samples.

Conclusion

Cancer pain is a detrimental symptom that threatens the health, well-being, and overall function of affected patients. Although many patients are prescribed analgesic regimens to alleviate the pain-related experience and associated symptoms, they often deviate from these recommendations for a wide array of reasons. The literature has identified several individual/family, provider, and system level covariates of nonadherence. However, little is understood about how patient beliefs related to analgesic treatment issues inform their objective adherence behaviors. This study attempts to fill this gap by employing innovative trade-off methodology techniques to describe patient belief utilities and correlating them with analgesic adherence behaviors. Findings are particularly relevant given the current context of opioid crisis and the need for more effective and equitable pain management strategies across settings and populations.

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Table 1. Key Terms.

- Analgesics: classified per the World Health Organization (1986, 1996, 2018) cancer pain ladder as follows:
    - Step 1: Nonopioids (e.g., nonsteroidal anti-inflammatories)
    - Step 2: Weak opioids (e.g., codeine, tramadol)
    - Step 3: Strong opioids (e.g., morphine, Fentanyl)
- Adherence: the extent to which a person's behavior (e.g., taking medication), corresponds with agreed recommendations from a health care provider (Sabate, 2001); often used interchangeably in the literature with the terms 'compliance' and 'concordance'
- Analgesic nonadherence: a behavioral deviation from a prescribed analgesic regimen; "a heterogenous construct that lends itself to varied results and interpretations based on the measures used or dimensions studied" (Meghani & Bruner, 2013, p. e23); operationalized through a number of subjective and objective measures
- Maximum differential scaling or 'MaxDiff': a type of discrete choice experiment that requires subjects to identify the 'least desirable' preference related to a given attribute, as well as the 'best' or 'most preferred' option available within a choice set (Finn & Louviere, 1992; Marley & Louviere, 2005); also known as "best-worst scaling" and used to identify the maximum difference in preference between the "best" and "worst" preferences available (Marley & Flynn, 2015)

- Medication Event Monitoring System (MEMS): objective metric of medication adherence through an electronic monitoring device technology (Aardex, Switzerland); uses a microprocessor chip implanted in a medication bottle cap to record the number of times the cap is removed in real-time; has been used in several studies to track analgesic adherence where the bottle cap openings serve as a proxy for analgesic taking behavior and are analyzed in comparison to prescribed regimens (Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Oldenmenger et al., 2007; Oldenmenger et al., 2017)

Table 2. Variables, Level of Data, and Variable Operationalization.

Variable	**Level of Data**	**Operationalization**
Demographics		
Age	Continuous	Selected from range
Gender	Categorical	1=male 2=female
Marital Status	Categorical	1=married 2=separated 3=divorced 4=widowed 5=never married
Religion	Categorical	1=Christian 2=Muslim 3=Jewish 4=other
Self-identified Race	Categorical	1=African American 2=Caucasian
Education/Years of Formal Schooling	Categorical	1=no schooling 2=elementary 3=high school 4=college/trade 5=more than college
Employment Status	Categorical	1=full-time outside home 2=part-time outside home 3=full-time at home

		4=part-time at home 5=retired 6=unemployed 7=other
Household Income	Categorical	1=less than 10k 2=b/w 20k and 30 k 3=b/w 20k and 30k 4=b/w 30k and 50k 5=b/w 50k and 70k 6=b/w 70k and 90k 7=greater than 90k
Insurance Type	Categorical	1=private 2=Medicaid 3=Medicare 4=other/VA/none 5=multiple
Health Literacy Score	Continuous	3-15
Social Support Amount Score	Continuous	0-9 (number of people identified)
Social Support Satisfaction Score	Continuous	1-6 (6=most satisfied)
<u>Disease-Related</u>		
Cancer Type	Categorical	1=lung 2=breast 3=GI 4=GU/reproductive

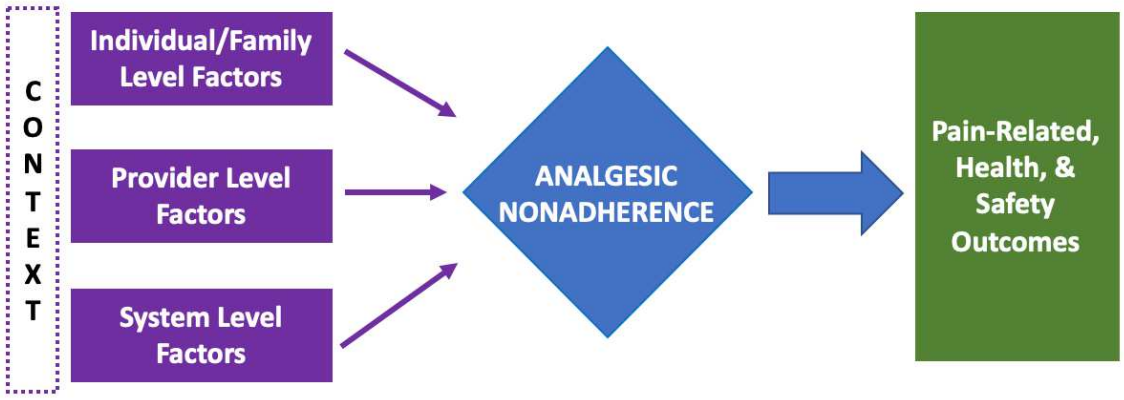
		5=multiple myeloma 6=other 7=multiple dx
Cancer Stage	Categorical	1=stage 1 2=stage 2 3=stage 3 4=stage 4
Length of Time Since Learning of Diagnosis	Continuous	1-120 (months)
<u>Pain-Related</u>		
Experience of Pain Present Due to Present Disease of Cancer	Categorical	1=yes 2=no 3=uncertain
Length of Pain Due to Present Disease of Cancer	Continuous	1-120 (months)
Average Pain in the Last Week	Continuous	0 (no pain) – 10 (worst imaginable pain)
Pain Functional Interference Score	Continuous	7-70
<u>Pain Treatment</u>		
Number of WHO Step 1 Analgesics	Continuous	0-4 (4 total medications possible)
Number of WHO Step 2 Analgesics	Continuous	0-4 (4 total medications possible)
Number of WHO Step 3 Analgesics	Continuous	0-4 (4 total medications possible)
Total number of analgesics (excluding co-analgesics)	Continuous	0-4 (4 total medications possible)

Co-analgesics	Continuous	0-4 (4 total medications possible)
Pain Management Index	Continuous	-3 -> +3 (negative=inadequate pain control, ≥0=adequate pain control)
Analgesic Preference		
MaxDiff: Cancer pain cannot be relieved with medications	Continuous	0-100%
MaxDiff: Many people with cancer get addicted to pain medicine.	Continuous	0-100%
MaxDiff: Pain medicine weakens the immune system.	Continuous	0-100%
MaxDiff: Pain medicine can keep you from knowing what's going on in your body.	Continuous	0-100%
MaxDiff: It is important to be strong by not talking about pain.	Continuous	0-100%
MaxDiff: Pain medicine makes you say or do embarrassing things.	Continuous	0-100%
MaxDiff: If doctors have to deal with pain, they won't concentrate on treating the cancer.	Continuous	0-100%
MaxDiff: It is easier to put up with pain than with the side effects that come from pain medicine.	Continuous	0-100%
MaxDiff: If you use pain medicine now, it won't work as well if you need it later.	Continuous	0-100%
MaxDiff: If I talk about pain, people with think I'm a complainer.	Continuous	0-100%

Barriers Questionnaire Total Effects Score	Continuous	27-162
Medication Side Effects Score	Continuous	8-78
Preference to Take Pain Medicine	Categorical	1=yes 2=no 3=uncertain
Analgesic Adherence		
How Much Pain Medication Taken in the Past Month (VAS_{dose})	Continuous	1(0%) – 11(100%)
Disease-Related (Other)		
Charlson Comorbidity Score	Continuous	0-13
Past History of Substance Abuse	Categorical	0=no 1=yes
Past History of Alcohol Abuse	Categorical	0=no 1=yes
Presence of Depression	Categorical	0=no 1=yes
General Health		
Level of General Health	Continuous	1(best) – 5(worst)
Number of Days in the Last 30 Days That Your Physical Health Was Not Good	Continuous	0-30 (days)
Number of Days in the Last 30 Days That Your Mental Health Was Not Good	Continuous	0-30 (days)

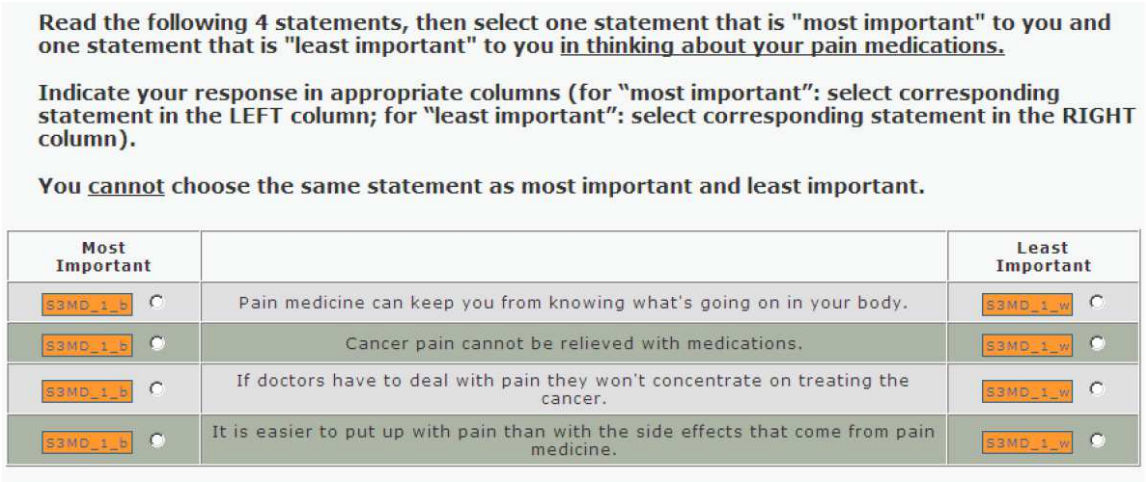
Health Literacy		
Health Literacy Score	Continuous	3-15

Figure 1. Conceptual Model of Analgesic Nonadherence for Cancer Pain (Rosa, Riegel, Ulrich & Meghani, 2020).



*This figure depicts the concept of analgesic nonadherence (center), as well as the concept's antecedents (left) and consequences (right).

Figure 2. Maximum Difference Survey Question from Parent Study with Instructions (Example 1).



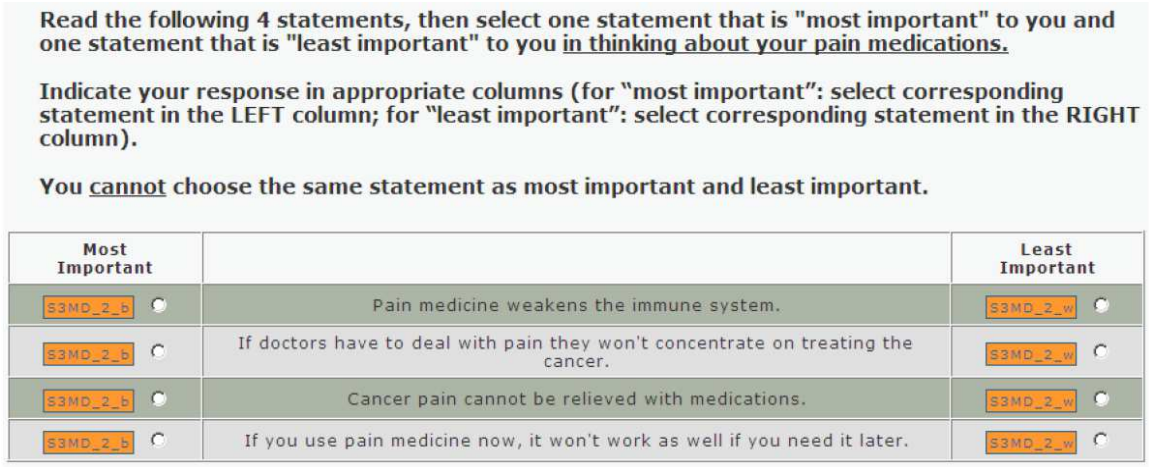
Read the following 4 statements, then select one statement that is "most important" to you and one statement that is "least important" to you in thinking about your pain medications.

Indicate your response in appropriate columns (for "most important": select corresponding statement in the LEFT column; for "least important": select corresponding statement in the RIGHT column).

You cannot choose the same statement as most important and least important.

Most Important		Least Important
S3MD_1_b	Pain medicine can keep you from knowing what's going on in your body.	S3MD_1_w
S3MD_1_b	Cancer pain cannot be relieved with medications.	S3MD_1_w
S3MD_1_b	If doctors have to deal with pain they won't concentrate on treating the cancer.	S3MD_1_w
S3MD_1_b	It is easier to put up with pain than with the side effects that come from pain medicine.	S3MD_1_w

Figure 3. Maximum Difference Survey Question from Parent Study with Instructions (Example 2).



Read the following 4 statements, then select one statement that is "most important" to you and one statement that is "least important" to you in thinking about your pain medications.

Indicate your response in appropriate columns (for "most important": select corresponding statement in the LEFT column; for "least important": select corresponding statement in the RIGHT column).

You cannot choose the same statement as most important and least important.

Most Important		Least Important
S3MD_2_b ○	Pain medicine weakens the immune system.	S3MD_2_w ○
S3MD_2_b ○	If doctors have to deal with pain they won't concentrate on treating the cancer.	S3MD_2_w ○
S3MD_2_b ○	Cancer pain cannot be relieved with medications.	S3MD_2_w ○
S3MD_2_b ○	If you use pain medicine now, it won't work as well if you need it later.	S3MD_2_w ○

CHAPTER 2

A Concept Analysis of Analgesic Nonadherence for Cancer Pain in a Time of Opioid Crisis[1]

[1] This chapter has been previously published: Rosa, W.E., Riegel, B., Ulrich, C.M., & Meghani, S.H. (2019). A concept analysis of analgesic nonadherence for cancer pain in a time of opioid crisis. *Nursing Outlook, 68*(1), 83-93. doi: 10.1016/j.outlook.2019.06.017 (Science Direct link to article: https://www.sciencedirect.com/science/article/pii/S0029655419301964?dgcid=author). Inclusion in this dissertation is protected in accordance with Elsevier's definition of personal use as described in their copyright policies (https://www.elsevier.com/about/policies/copyright).

ABSTRACT

Background: Pain is one of the most common symptoms identified along the cancer trajectory. Among patients with moderate to severe cancer pain, nonadherence to prescribed analgesics may complicate treatment plans and exacerbate pain severity. Nonadherent behaviors are likely due to a number of individual/family, provider, and system level factors and may lead to negative pain-related outcomes. The purpose of this concept analysis is to clarify the concept of analgesic nonadherence or cancer pain and qualify its utility in the context of the opioid crisis.

Method: Walker and Avant's (2019) method for concept analysis was used. We integrated empirical evidence, relevant literature, and sociopolitical considerations realted to the opioid crisis to provide critical and timely analysis. Data were collected from a search of PubMed, CINAHL, PsychINFO, and Scopus. The search yielded 418 individual records. Empirical articles using quantitative and qualitative methodologies pertaining to analgesic nonadherence for cancer pain in adult outpatient settings, written in English, with an abstract, and published between 2010 and 2018 were considered. Other relevant literature sources were used if additional criteria were met. A total of 33 records were selected for detailed review.

Findings: Few studies link analgesic nonadherence to patient outcomes highlighting a significant literature gap. Given the available evidence, a definitions for analgesic nonadherence is proposed for future use in research, education, practice, and policy settings.

Discussion: The paucity of empirical data combined with the implications of the opioid crisis and conflicting pain management guidelines create uncertainty about the utility of analgesic nonadherence. The concept of analgesic nonadherence warrants further normative and empirical research to clarify the role of opioids and the meaning of nonadherence in shaping pain-related outcomes within the current sociopolitical environment.

A Concept Analysis of Analgesic Nonadherence for Cancer Pain in a Time of Opioid Crisis

Introduction

According to the Centers for Disease Control and Prevention (CDC; 2018), an estimated 68% of the 70,200 drug overdose deaths in the United States (US) in 2017 involved the use of an opioid. In fact, the number of drug overdose deaths that implicated opioids increased six-fold between 1999 and 2017 (CDC, 2018). In the current climate of the opioid addiction epidemic, various stakeholders are calling for tighter opioid access policies, more rigorous prescribing standards, and increasingly tailored patient and community education mechanisms (Christie et al., 2017; National Academies of Sciences [NAS], 2017; National Academy of Medicine, 2017). While there has been robust focus on clinician implications related to responsible opioid stewardship, we still lack clear empirical understanding about the factors that correlate with patients' use of analgesics.

Opioids remain a keystone of moderate to severe cancer pain management (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; World Health Organization [WHO], 2018), despite discrepant pain management guidelines that complicate prescribing practices (Meghani & Vapiwala, 2018). According to these guidelines, many patients with moderate to severe cancer pain require complex analgesic regimens, at times including a combination of nonopioids, short- and long-acting opioids, and adjuvant prescriptions, to effectively alleviate pain and improve overall function. Even though such medication treatment plans are often warranted, many patients deviate from recommended analgesic regimens or stop taking them altogether.

Patient nonadherence to prescribed analgesics for cancer pain may compromise a number of pain-related, health, and safety outcomes (Lee et al., 2015; Manzano, Ziegler, & Bennett, 2014; Meghani & Knafl, 2016). Cancer patients demonstrate nonadherent behaviors for a variety of reasons, ranging from individual and family factors (Lee et al., 2015; Meghani & Bruner, 2013; Meghani, Chittams, Hanlon, & Curry, 2013; Meghani & Knafl, 2017) to provider and system level barriers (Bryan, De La Rosa, Hill, Amadio, & Wieder, 2008; Schumacher et al., 2014a; Wieder, Delarosa, Bryan, Hill, & Amadio, 2014; Xu, Luckett, Wang, Lovell, & Phillips, 2018).

The purpose of this concept analysis is to clarify the meaning of analgesic nonadherence for cancer pain and its use in the literature with respect to the US opioid crisis. We employ the Walker and Avant (2019) method to deconstruct this concept and articulate future implications for practice, research, education, and policy. To these authors' knowledge, this is the first conceptual analysis of nonadherence specific to analgesics for cancer pain. A clearer understanding of analgesic nonadherence is crucial in order to streamline pain management plans and best assist patients in effectively mitigating their cancer pain burdens in the future.

Background and Significance

The Pain Experience

Pain is a burdensome symptom affecting patients across the cancer trajectory. A recent systematic review and meta-analysis of 112 studies on pain (n=63,533) and pain severity (n=32,261) suggests an estimated two-thirds of patients with advanced cancer report "some" pain, and up to 38% of patients report their pain as "moderate" or "severe"

(van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016). In a longitudinal study exploring cancer survivors' symptom burden at one-year postdiagnosis (n=4,903), Shi and colleagues (2011) noted that pain was rated as one of the top three symptoms negatively impacting health-related quality of life. The authors of several literature syntheses and landmark reports conclude that cancer pain control may be suboptimal for many populations and call for enhanced mechanisms to improve equitable access and delivery of pain care services (Institute of Medicine [IOM], 2003; Meghani, Byun, & Gallagher, 2012; NAS, 2017; Xu et al., 2018).

Analgesic Use

A number of factors influence analgesic use. Individual beliefs, preferences, and values are likely to inform nonadherent behaviors. For instance, patients' beliefs about analgesics may act as barriers to adherence, such as worries that these medications will cause physiological or immune system harm or will lead to addiction (Liang, Tung, et al., 2013; Simone, Vapiwala, Hampshire, & Metz, 2012; Ward et al., 1993). Patient affective factors, such as emotional distress or anxiety, have been shown to correlate with nonadherence choices (Jacobsen et al., 2014). In addition to patients, their families and caregivers also play a significant role in determining analgesic use and the level of demonstrated adherence (Valeberg, Miaskowski, Paul, & Rustoen, 2016). In fact, distinct family dynamics and family member hesitancy to use analgesics may mediate patient adherence behaviors (Lee et al., 2015; Schumacher et al., 2014). The evidence points to several other considerations required to grasp the full breadth of the concept, such as the quality of clinician-patient communication and analgesic accessibility (Thinh et al.,

2018). Other elements include socioeconomic status and structural barriers, including insurance coverage (Bryan et al., 2008; Valeberg et al., 2008; Wieder et al., 2014).

The Sociopolitical Milieu

The opioid crisis compounds the phenomenon of analgesic taking behaviors throughout the national healthcare system. Across the United States, opioid-related events led to a 64.1% increase of inpatient hospital stays and a 99.4% increase in emergency department visits between 2005 and 2014 (Rudd, Seth, David, & Scholl, 2016); and in 2015, opioid-related deaths led to overall economic costs estimated at $504 billion or roughly 2.8% of gross domestic product (The Council of Economic Advisors, 2017). The crisis marks an era of policy flux, rigorous scientific debate, and multi-agency collaboration to balance the dual loyalties of reducing the individual burden of cancer pain while minimizing the mounting social sequelae of opioid use in America (Johnson et al., 2018; Lamar, 2018; NAS, 2017; National Institutes of Health [NIH], 2018; US Department of Health and Human Services, 2017). An additional complicating feature is the recent identification of the critical divide between cancer pain management guidelines of leading pain organizations (Meghani & Vapiwala, 2018). These inconsistent standards are due to the daunting lack of accumulated empirical evidence related to cancer pain management (Meghani & Vapiwala, 2018; NIH, 2014). The concept of analgesic nonadherence is likely to be best understood by accounting for both the context of the opioid crisis and the above noted paucity of empirical cancer research.

Method

Walker and Avant's (2019) approach to concept analysis (Box 1) is employed to construct a precise conceptual definition of analgesic nonadherence for cancer pain for future theoretical and empirical consistency. This method was selected due to its inclusion of example cases, offering a pragmatic application of the conceptual aspects, which is essential given the sociopolitical background previously mentioned. Additionally, this method stresses an iterative approach, promoting continuous exploration and clarification throughout the process. Finally, since concepts are tentative in nature, it is crucial to be aware of the cultural, contextual, and social factors that contribute to the current understanding of the concept at hand (Walker & Avant, 2019). Therefore, this method allows the reader to relate analysis findings directly to the health and policy dynamics of the US opioid crisis.

The initial search in PubMed used the MeSH search ('neoplasms' OR 'cancer' OR 'cancer pain' OR 'cancer related pain') AND ('treatment adherence and compliance' OR 'medication adherence' OR 'patient compliance') AND ('analgesics' OR 'analgesics, opioids' OR 'narcotics'). Further searches in CINAHL, PsycINFO, and Scopus used the above terms as keywords. Search terms were defined in collaboration with a librarian at the University of Pennsylvania Biomedical Library, Philadelphia, Pennsylvania. The search yielded 418 individual records; duplicates, articles in languages other than English, and those without an abstract were excluded. Empirical articles using quantitative and qualitative methodologies and pertaining to analgesic nonadherence for cancer pain in adult inpatient and outpatient settings, written in English, with an abstract,

and published between 2010 and 2018 were considered. This time period was chosen because it spans the current opioid crisis in the United States according to related literature that emerged during its peak in 2010.

Relevant internationally gathered evidence was employed if it contributed distinct considerations regarding the concept not addressed in US-based literature. Organizational pain management guidelines and recommendations, as well as seminal documents outside of the proposed time frame that continue to influence current analgesic policy and practice were included. Non-empirical sources included records from Merriam Webster dictionary (n=2); WHO (n=3); NCCN (n=1); and previous related concept analyses (n=2). After applying exclusion criteria (Figure 1), a total of 33 records were selected for detailed review.

Results

Uses of the Concept

The terms *adherence* and *nonadherence* are often used interchangeably in the literature and are facets of the same phenomenon. Other terms such as *noncompliance* and *nonconcordance* have been employed synonymously with nonadherence. The Merriam-Webster dictionary defines *nonadherence* as "a lack of adherence" (Merriam-Webster, n.d.-b). It is, therefore, essential to grasp the meaning of *adherence. Adherence* is "the act, action or quality of adhering" or "steady or faithful attachment" (Merriam-Webster, n.d.-a). Previous concept analyses of *adherence* define it as a "complex, multidimensional concept impacted by essential elements such as autonomy, self-determination, self-efficacy, and communication" (Gardner, 2015, p. 100). Other authors

emphasize the concept should be considered through a patient-centered lens, incorporating an individual's context in how it is evaluated (Alikari & Zyga, 2014). The WHO (2003) identifies patients' *active* participation in medical plan development as a primary factor that differentiates *adherence* from the historical notion of *compliance*. The WHO (2003) defines *adherence* as "the extent to which a person's behavior – taking medication, … executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (p. 3).

Analgesics are classified using the WHO (1986, 1996, 2018) cancer pain ladder and includes step 1 - nonopioids (e.g., nonsteroidal anti-inflammatories); step 2 - weak opioids (e.g., codeine, tramadol); and step 3 – strong opioids (e.g., morphine, Fentanyl). Opioids are further classified as long-acting, used to obtain background analgesia for chronic cancer pain, and immediate-release, taken to treat breakthrough pain and deliver a quicker onset but shorter duration of pain relief (NCCN, 2019). Some studies include a patient's use of *coanalgesics*, such as antidepressants, anticonvulsants, or corticosteroids, in understanding predictors of overall nonadherence to pain management recommendations (Schumacher et al., 2014b). Researchers may focus on adherence related to one particular step of the cancer pain ladder, such as strong opioids (Chancellor, Martin, Liedgens, Baker, & Muller-Schwefe, 2012); assess differences in rates of adherence between nonopioids and opioids (Oldenmenger et al., 2017); focus primarily on short- or long-acting opioids (Yoong et al., 2013); or include a broad range of analgesic types (Simone et al., 2012).

Analgesic nonadherence has been recognized as "a heterogenous construct that lends itself to varied results and interpretations based on the measures used or dimensions studied" (Meghani & Bruner, 2013, p. e23). How analgesic nonadherence is empirically represented varies. For example, some studies define analgesic nonadherence using subject self-report (Meghani & Bruner, 2013); computed rates of adherence based on proportions of prescribed doses taken during a given time period (Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Rhee et al., 2012); or the number of patients found to be taking medications as recommended during follow-up appointments (Wieder et al., 2014). Other researchers study the proportion of doses taken correctly across a given number of days and within given time intervals per day in relation to medical recommendations (Oldenmenger et al., 2017) or the amount of opioid taken in comparison to the amount of opioid prescribed (Nguyen et al., 2013).

Defining Attributes

Attributes are the qualities or features most commonly associated with a concept (Walker & Avant, 2019). The primary defining attribute of analgesic nonadherence is a behavior that establishes deviation from a prescribed regimen and may be the result of both conscious and unconscious influences (Meghani & Bruner, 2013; WHO, 2003). Such behaviors include filling prescriptions, taking medications as prescribed, attending scheduled appointments, adopting health behavior change, etc. (WHO, 2003). These behaviors have been identified as intentional, unintentional, and/or temporal. *Intentional* nonadherence is a deliberate choice not to follow a given recommendation; an active decision reflects a patient's desire to stop taking their analgesic (Morisky, Green, &

Levine, 1986). *Unintentional* nonadherence is an unconscious, relatively passive process that results in similarly noted behavior (Morisky et al., 1986). Temporality is an important attribute (Meghani & Knafl, 2016). While some nonadherent behaviors were found to be habitual, many were influenced by temporal choices and priorities, fluctuating in accordance with changes to patients' daily, weekly, or monthly schedules (Manzano et al., 2014).

Antecedents of Analgesic Nonadherence

Per Walker and Avant (2019), antecedents are events that must be in place prior to the occurrence of the concept whereas consequences reflect the outcomes of the concept. For clarity, antecedents have been categorized as individual/family level, provider level, and system level.

Individual/family level. Identifying patients' main anchors for decision-making is central to understanding the driving forces of nonadherent behaviors. In a study of 207 outpatient oncology subjects, about 41% maintained an expectation of pain relief that primarily determined analgesic decision-making; 11% were most concerned with the type of analgesic used; roughly 28% were driven by multifactorial determinants including pain relief and the type and severity of side-effects; and 21% were influenced predominantly by the type of side effects experienced (Meghani & Knafl, 2017). Longitudinal qualitative findings echo that the extent to which side effects interfere with a patient's life directly coincides with nonadherence behaviors (Manzano et al., 2014). Researchers using a phenomenological method to elicit the illness narratives of cancer patients (n=18) suggested that self-perceived benefits of following an analgesic regimen, subjective self-

efficacy, and trust in healthcare providers improved adherence; denial of pain as a symptom of the disease process posed a barrier (Torresan et al., 2015).

Such concerns, in addition to beliefs and preferences have been well-documented predictors of nonadherent behavior to analgesic regimens, particularly to opioids (Chancellor et al., 2012; Rhee et al., 2012). This includes patients' concerns about the physiological effects of opioids and worry about dependence or addiction (Jacobsen et al., 2014; Liang, Chen, et al., 2013; Simone et al., 2012), as well as a belief that doctors should focus on cancer treatment rather than pain (Rhee et al., 2012). Families and caregivers play a pivotal role in this phenomenon. Family hesitancy to use analgesics has been found to mediate patients' barriers and patients' adherence (Lee et al., 2015). Furthermore, family characteristics directly impact the home environment in which patients live and anchor their analgesic decision-making processes (Schumacher et al., 2014b).

Various sociodemographic variables have been identified to play a predictive role in opioid nonadherence. Studies disagree whether males or females demonstrate nonadherent behaviors more frequently (Liang, Wu, Tsay, Wang, & Tung, 2013; Liang, Wang, et al., 2013; Nguyen et al., 2013). The same empirical variation occurs in reference to age, with some investigators noting increased nonadherence among younger cancer patients (Koyyalagunta et al., 2018); however, older patients may be more likely to intentionally stop taking medications when they feel better (Meghani & Bruner, 2013). Other predictors, including income, education and health literacy levels, and level of prescription coverage have been identified as significant (Meghani & Knafl, 2017;

Wieder et al., 2014). It appears challenging for patients to take scheduled analgesics at the correct time intervals due to scheduling issues, forgetfulness, and the complexities of daily life (Oldenmenger et al., 2017). Of note, increased use of complementary and alternative medicine for cancer pain management was positively correlated with unintentional nonadherence (Meghani & Bruner, 2013).

Perhaps one of the most glaring sociodemographic antecedents is race - even when controlling for insurance and socioeconomic status (IOM, 2003). African-Americans are found to experience increased severity of pain more frequently than White counterparts (Martinez, Snyder, Malin, & Dy, 2014). Additional studies have shown that African-Americans are more likely to make nonadherence choices based on the "type of side effects" experienced rather than "pain relief" (Meghani et al., 2013; Meghani & Knafl, 2017), which means nonadherence may be more common in African-American patients due to a higher rate of side effects from inappropriately prescribed analgesics (Meghani et al., 2014).

Provider Level. Prescribing practices are a major aspect of provider level antecedents. Patients prescribed around-the-clock (ATC) analgesics other than long-acting opioids were more inconsistently adherent (Meghani & Knafl, 2016). Racial disparity is also a factor at the provider level. African-Americans may receive inconsistent or erroneous pain assessments by healthcare providers (Wandner et al., 2014) and are less likely to be prescribed long-acting opioids for pain relief (Meghani et al., 2015). Meghani et al. (2014) suggest race is a strong predictor of both the type of opioid prescribed and the severity of analgesic side effects incurred. For example,

African-Americans have 71% lower odds than Whites of being prescribed oxycodone versus morphine in the setting of chronic kidney disease (CKD) (Meghani et al., 2014). This is crucial as morphine accumulates toxic renal metabolites in the setting of CKD that exacerbate negative side effects and may promote nonadherence. Other minorities, such as Hispanic patients, have also been noted to be prescribed fewer long-acting opioids than Whites (Meghani et al., 2015; Wieder et al., 2014).

System Level. Researchers' interviews with cancer patients (n=42) and family caregivers (n=20) point to a number of system level antecedents, including complex clinical care, reimbursement, and analgesic regulation processes; obtaining analgesics; and the patient/family burden of coordinating care and assuring effective communication among different providers (Schumacher et al., 2014a). Insurance and prescription coverage is a substantive predictive factor, with less coverage often afforded racial and ethnic minorities (Wieder et al., 2014).

Consequences of Analgesic Nonadherence

There are notably few studies that actually link nonadherence to patient or health utilization outcomes. This is a significant gap in the literature. Notwithstanding, the consequences identified impact myriad life domains. In a cross-sectional and descriptive study of 176 patient-caregiver dyads, patients with lower adherence levels who lived in settings where families were hesitant to use analgesics reported an increased severity of pain (Lee et al., 2015). Among a sample of 196 outpatient oncology subjects taking around-the-clock analgesics in a three-month prospective observational study, an interaction of strong (WHO step 3) opioids and inconsistent adherence was the strongest

predictor of hospitalization (Meghani & Knafl, 2016). Finally, researchers using an exploratory longitudinal design and qualitative research methods found that patients (n=11) who experienced increased pain secondary to analgesic nonadherence sustained negative impacts to both physical and social functioning, as well as overall quality of life (Manzano et al., 2014).

Model Case

Take the case of a 40-year-old male diagnosed with stage III colon cancer. He is prescribed long-acting oxycontin 20mg by mouth twice daily and oxycodone 5-10 mg by mouth every 4 hours as needed for breakthrough spinal pain due to metastatic disease. He is terrified of becoming addicted to opioids despite no relevant family or personal history and he consistently chooses to forego his oxycontin. The patient will take his oxycodone only when his pain is unbearable. His wife is also adamant he not take opioids due to the news of the national crisis and fear her husband may suffer an overdose. His current prescriber insists on him following the regimen as recommended and provides standardized education in the form of a brochure intended to alleviate his worries. Of note, this is his first time seeing a pain specialist. His oncologist did not think opioids were indicated and suggested nonopioid analgesics to manage the patient's cancer pain since he is not currently receiving active cancer treatment. This patient's intentional nonadherence has led to multiple emergency room visits for pain crises and a rapid deterioration of quality of life since he is unable to eat, sleep, or work secondary to uncontrolled pain.

This case reflects the ways a patients' salient concerns, family hesitancy, prescribers' lack of clarity regarding guidelines, and depersonalized education intersect to impact a patient's nonadherence behaviors (Lee et al., 2015; Meghani & Knafl, 2017; Meghani & Vapiwala, 2018) and subsequent increase in healthcare utilization (Meghani & Knafl, 2016). Additional cases might describe other challenges, such as analgesic access given insurance coverage gaps, ineffective coordination between healthcare services, or how race has been shown to predict nonadherence (Meghani et al., 2014; Schumacher et al., 2014a; Wieder et al., 2014).

Related Case

According to Walker and Avant (2019), a related case may depict some of the attributes of a concept but also differs from them when examined more closely; a particularly relevant approach to this phenomenon. Take the case of a 34-year-old undomiciled African-American woman recently discharged from a public urban hospital for uncontrolled pain secondary to her advanced breast cancer. Her primary insurance is Medicaid. She experienced confusion and nausea to inpatient trials of morphine and then oxycodone for pain control, finally achieving a desirable response to Fentanyl. While admitted to the hospital, she felt her pain was being inappropriately managed and inconsistently assessed. In addition, she has CKD and had been resistant to taking morphine for this reason. She is ultimately discharged with prescriptions for a 100 microgram/hour transdermal Fentanyl patch to be changed every 72 hours and hydromorphone 8-12mg by mouth every 3 hours as needed for breakthrough pain. She denies side effects and endorses tolerable pain on this regimen. After discharge, she is

told by the local pharmacist that Medicaid will not pay the cost of her prescriptions and she must use a cheaper medication, such as morphine. The licensed independent practitioner at her oncologist's office writes the new prescription that Medicaid will cover. The patient uses her remaining Fentanyl and hydromorphone, foregoes taking the morphine due to the adverse effects she previously experienced, and ends up in the emergency room later that week in a pain crisis. It takes an additional week to gain insurance approval for the analgesic regimen that works best for her to ensure a safe discharge – a structural barrier that prevents adherence to the regimen as prescribed.

System-wide challenges, such as analgesic access given insurance coverage issues and ineffective coordination between prescribers and various healthcare services, makes adherence impossible (Schumacher et al., 2014a; Wieder et al., 2014). This case also illustrates how race has been shown to predict nonadherence based on the inappropriate use of opioids and inaccurate assessment of pain (Meghani et al., 2014).

Empirical Referents

Empirical referents are the means through which the concept can be recognized and its defining attributes measured (Walker & Avant, 2019). Assessing the underlying factors that influence nonadherence and determining their basis is essential. For example, eliciting intentional versus unintentional processes that result in nonadherent behavior have suggested distinct correlates and decision-making heuristics for each category (Meghani & Bruner, 2013; Morisky et al., 1986). Objective measures used in the analgesic adherence literature include the use of an electronic medication event monitoring system, a tool that records the number of analgesic bottle openings as a proxy

for adherence, subsequently correlating findings with prescribed analgesic frequency (Meghani et al., 2015; Oldenmenger et al., 2017).

Incorporating self-reported levels of adherence may capture a key element in unraveling how nonadherence presents in the cancer pain setting. It has been noted that subjective analgesic-related beliefs poorly explain objective analgesic taking, which is influenced more strongly by clinical pain variables (e.g., severity of adverse effects, pain relief, etc.) (Meghani & Knafl, 2016; Meghani et al., 2015). However, subjective measures may be helpful to understand medication-taking habits, comparing objective data to self-reported adherence for increased validity of findings, and recognizing the various preferences and behaviors that interact to result in nonadherence (Meghani et al., 2013; Meghani & Knafl, 2017)

Figure 2 provides a model to depict this concept's defining attributes, antecedents and consequences, and empirical referents.

Discussion

This analysis has sought to clarify the concept of analgesic nonadherence for cancer pain and its use in the literature given the current sociopolitical implications of the opioid crisis. In sum, the literature falls short, leaving us with more questions than answers. Only a handful of studies have made the link between analgesic nonadherence and outcomes, which include increased pain severity, higher rates of hospitalization, and decreased overall quality of life (Lee et al., 2015; Manzano et al., 2014; Meghani et al., 2014; Meghani & Knafl, 2016). Ultimately, 'what' defines optimum adherence behavior is not clear. This paucity of evidence combined with the practice and policy shifts

resultant of the opioid crisis invite a new commitment to further empirical studies in this area. Based on this analysis - while also considering the implications of the current national context - a more inclusive definition of analgesic nonadherence for cancer pain is posed: *Patient deviation from a prescribed analgesic regimen for cancer pain, predicted by highly contextual factors within individual/family and societal domains and potentially complicating both one's symptom burden and a variety of health outcomes.*

There is insufficient reliable evidence to denote a value judgment on analgesic nonadherence as "good" or "bad". However, initiatives and policies aimed at mitigating the crisis are complicating patient access, decreasing the willingness of prescribers to give opioids, and limiting prescription coverage for patients requiring analgesics, ultimately impacting patients' use (Johnson et al., 2018; Lamar, 2018; NAS, 2017). The question of how to balance social welfare while upholding the moral obligation to alleviate pain and suffering is at the center of this crisis (NAS, 2017), as well as inherent to the antecedents of analgesic nonadherence faced by patients.

Current cancer pain management guidelines are limited by a dearth of empirical research on long-term opioid use to support best practices; the result is conflicting recommendations from a number of organizations (Meghani & Vapiwala, 2018; Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2019). Although many guidelines identify opioids as foundational to effective relief for moderate to severe cancer pain (NCCN, 2019; Paice et al., 2016; WHO, 2018), the CDC discourages opioid use as a first-line treatment for cancer survivors, who are likely to continue to experience pain long after active cancer treatment has concluded (Dowell, Haegerich, & Chou, 2016;

Shi et al., 2011). These competing guidelines are likely to cause confusion among clinicians, placing patients at risk for subpar, ineffective, and/or risky consequences (Meghani & Vapiwala, 2018). In understanding analgesic nonadherence, we must ask: Adherence toward what end? Adherence based on which guidelines and considering what literature?

Specifically, Meghani and Vapiwala (2018) point out conflicting recommendations regarding the use of long-acting and immediate-release opioids, which may also affect adherence behaviors. For instance, they point out that per the NCCN (2019), long-acting opioids to provide background analgesia should be used in combination with immediate-release opioids for breakthrough pain; however, the CDC (Dowell et al., 2016) discourages long-acting opioid use, particularly when immediate-release opioids are concurrently prescribed. A crucial question is: What does analgesic nonadherence mean in the context of the CDC opioid guidelines, particularly in the absence of empirical data for this patient population? In other words, how do providers ensure timely, effective pain management by addressing adherence concerns for cancer patients at risk for poor pain control, especially in settings that employ inappropriately applied guidelines for the population at hand?

The continued study of analgesic nonadherent behaviors in the cancer pain field given guideline discrepancies and emergent policy debates will be essential to improve care for affected patients. Furthermore, several studies focus specifically on adherence to ATC pain regimens (Meghani & Knafl, 2016; Yoong et al., 2013); which may warrant distinct considerations from those patients prescribed only immediate release analgesics.

In the trend toward prescribing fewer long-acting scheduled analgesics and using primarily immediate release medications, the concept of analgesic nonadherence and its consequences becomes vastly unclear. This paradox requires further investigation to determine similarities and differences between adherence to both long-acting and immediate release analgesics. .

Patients' nonadherent behaviors have been observed in the literature using various patient-reported surveys and instruments and technologies (Meghani & Bruner, 2013; Meghani et al., 2013), which makes it difficult to understand and explicate nonadherence and underlying decision-making processes across studies. Further exploration is needed to test the interplay of objective and subjective nonadherence measures, as well as qualitative data that seeks to tease apart the underlying patterns that result in nonadherent behavior. Additional research might further explore how analgesic adherence choices are made and the utilities and tradeoffs employed by patients in the decision-making process.

Tailored education for patients, families, and prescribers regarding safe and effective analgesic use may assist in promoting that the holistic determinants of nonadherence are addressed. This requires attention to patient-centric models that elicit individual preferences and values, mitigate risks, and empower prescribers to correctly apply guidelines. Oldenmenger and colleagues (2018) systematically reviewed 28 randomized controlled trials (n=4,735), showing that standard patient education programs to reduce analgesic nonadherence may be effective but are correlated with a significant pain improvement outcome in less than 20% of all cancer pain patients. These results highlight additional research gaps in this area.

Overall imperatives include the improvement of pain control, function, and quality of life and ultimately determining if heightened scholarly focus on nonadherence has a meaningful role in meeting these outcomes. Furthermore, available evidence is inconclusive about how to best decrease nonadherent behaviors and understand its role in predicting patient outcomes.

Limitations

The findings of this concept analysis should be considered in light of the following limitations. While MeSH terms were used, the diversity of terms chosen to describe nonadherent behavior may have resulted in the omission of some articles during the literature review. Though a limited number of organizational recommendations prior to 2010 were included in the analysis due to their continued influence on analgesic management of cancer pain and adherence, the selected time frame of the search criteria (2010-2018) may have overtly limited additional meaningful records for this phenomenon which possesses an already extensive literature gap. While this analysis was approached with consideration to the US opioid crisis, broader inclusion criteria in the future might invite a different understanding of the concept when explored through the lens of opioid use and availability in the international arena and across diverse cultures.

Conclusion

Cancer pain impacts patients and families by limiting physical and social function, negatively impacting quality of life, and complicating already taxing oncology treatment plans. Analgesic nonadherence in the current sociopolitical milieu deserves

further scholarly dialogue and research to further elicit its relationship to cancer pain; in short, the role of nonadherence in shaping clinical outcomes must continue to be addressed. Ultimately, a more detailed understanding of the physiological mechanisms of analgesic nonadherence may lead to interventions at individual and aggregate levels that support patients in employing pain medication regimens to more effectively meet their needs.

It is impossible to sever the complexities related to the opioid crisis from factors that influence analgesic nonadherence. In fact, the opioid crisis is a crucial and underexplored antecedent of analgesic nonadherence. The context that birthed the addiction epidemic, including the beliefs, preferences, and values of both providers and patients, continues to evolve in an era of stigma and policy fluctuation. The full impact of the role analgesic nonadherence plays in cancer pain management, particularly within this current sociopolitical milieu, needs further critical understanding.

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Box 1. Concept Analysis Process (adapted from Walker & Avant, 2019).

1. Select a concept.
2. Determine analysis aims and purpose.
3. Identify all discoverable uses of the concept.
4. Describe the concept's defining attributes.
5. Specify antecedents and consequences of the concept.
6. Articulate a model case.
7. Identify a related case.
8. Define empirical referents.

Figure 1. Inclusion/Exclusion Flowchart.

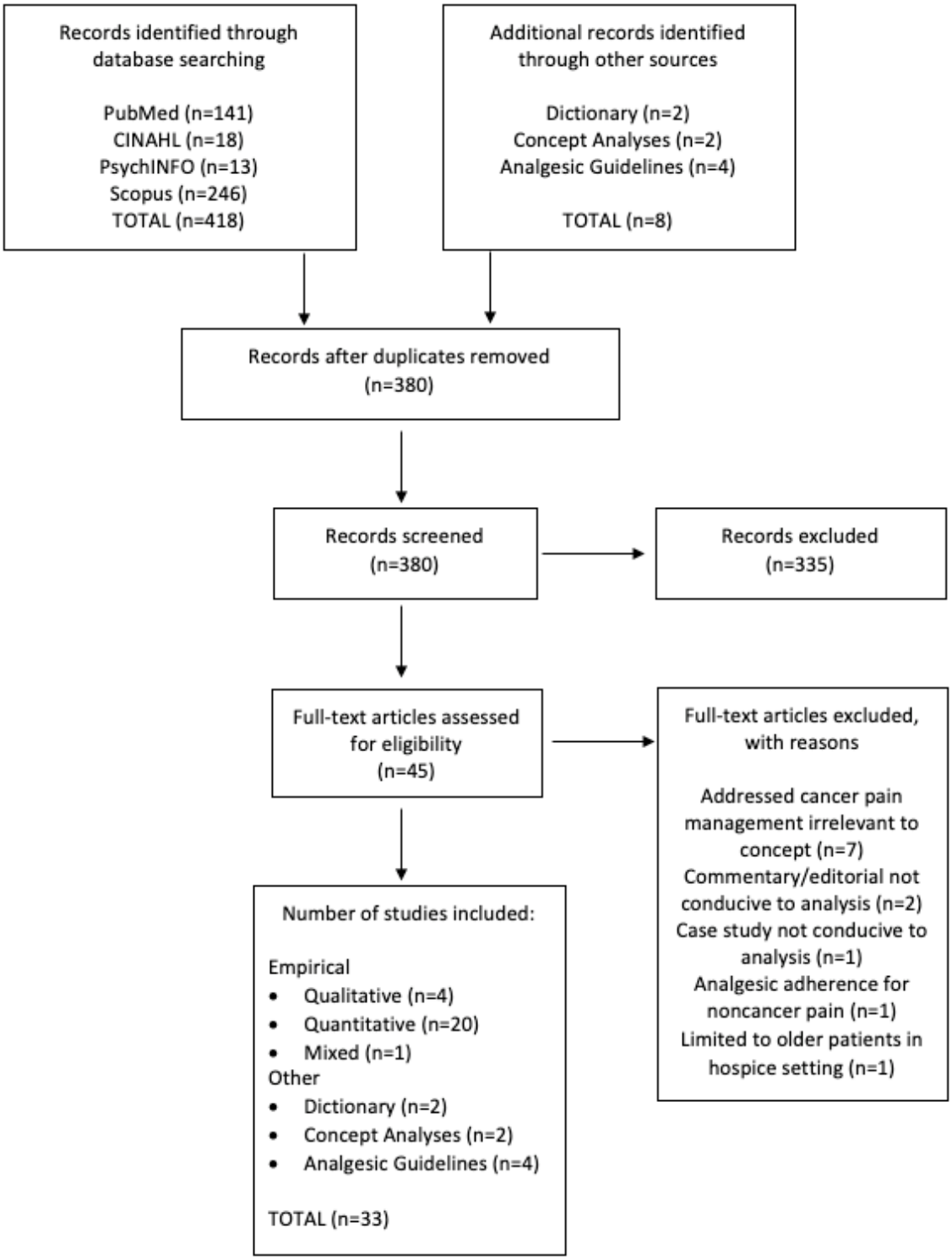
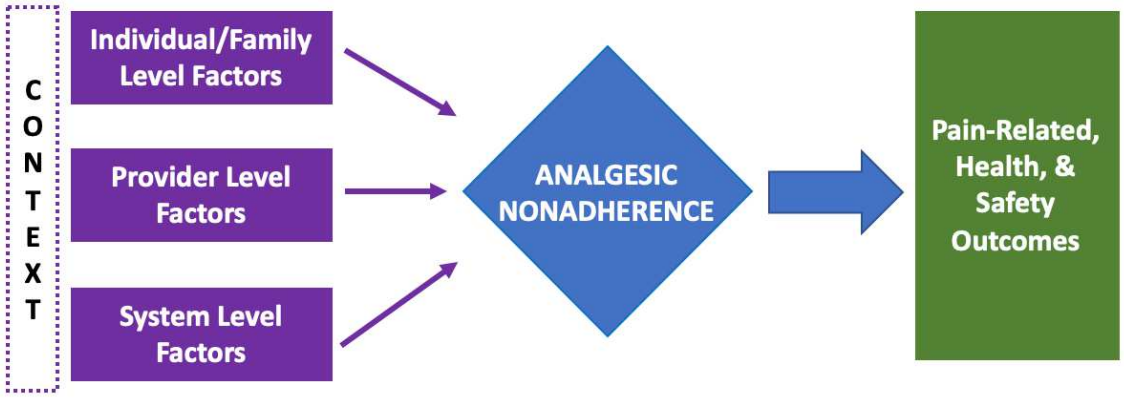


Figure 2. Conceptual Model of Analgesic Nonadherence for Cancer Pain (Rosa, Riegel, Ulrich, & Meghani, 2020)



*This figure depicts the concept of analgesic nonadherence (center), as well as the concept's antecedents (left) and consequences (right).

CHAPTER 3

Patient Trade-Offs Related to Analgesic Use for Cancer Pain: A MaxDiff Analysis Study[2]

[2] This chapter has been previously published: Rosa, W.E., Chittams, J., Riegel, B., Ulrich, C.M., & Meghani, S.H. (2019). Patient trade-offs related to analgesic use for cancer pain: A MaxDiff analysis study. *Pain Management Nursing.* Epub ahead of print. doi: 10.1016/j.pmn.2019.07.013. (Science Direct link to article: https://www.sciencedirect.com/science/article/abs/pii/S1524904219300980?dgcid=rss_sd_all). Inclusion in this dissertation is protected in accordance with Elsevier's definition of personal use as described in their copyright policies (https://www.elsevier.com/about/policies/copyright).

ABSTRACT

Purpose: Many patients with cancer pain deviate from prescribed analgesic regimens. Our aim was to elicit the trade-offs patients make based on their beliefs about analgesic use and rank utilities (importance scores) using maximum difference (MaxDiff) scaling. We also investigated if there were unique clusters of patients based on their analgesic beliefs.

Methods: This was a secondary analysis of a three-month, prospective observational study. Patients (N=207) were self-identified African Americans and Whites, >18 years, diagnosed with multiple myeloma or solid tumor, and were prescribed at least one around-the-clock analgesic for cancer pain. MaxDiff analysis allowed us to identify patients utilities. Second, a cluster analysis assisted in ranking how analgesic beliefs differed by groups. Third, clusters were described by comparing key sociodemographic and clinical variables.

Results: Participants' beliefs were a significant factor in choices related to analgesic use (chi-square = 498.145, $p < .0001$). The belief, 'Pain meds keep you from knowing what is going on in your body', had the highest patient endorsement. Two distinct clusters of patients based on analgesic beliefs were identified; 'knowing body' was ranked as top priority for both clusters. The belief that cancer patients become addicted to analgesics was moderately important for both clusters. Severity of side effects was the only key variable significantly different between clusters ($p = .043$).

Conclusions: Our findings support tailored pain management interventions that attend to individual beliefs about cancer pain and analgesic use. Future research should explore the relationship between analgesic utilities, actual analgesic taking behaviors, and how they impact patients' cancer pain outcomes.

Patient Trade-Offs Related to Analgesic Use for Cancer Pain: A MaxDiff Analysis Study

The health and policy implications of the current opioid addiction epidemic require an increased scientific focus on tailored and person-centered pain management interventions (National Academies of Sciences, 2017; National Academy of Medicine, 2017). This is particularly relevant for patients with cancer, given a well-documented high prevalence of cancer pain. In a systematic review and meta-analysis of 112 studies on pain and pain severity, roughly two-thirds of advanced cancer patients reported 'some pain' and about 38% of all cancer patients described their pain as 'moderate' to 'severe' (van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016). Pain has also been endorsed as one of the top three most burdensome symptoms negatively affecting health-related quality of life for patients (N=4,903) in the year following cancer diagnosis (Shi et al., 2011). In this time of opioid crisis, there are noted inconsistencies in pain management guidelines and competing priorities among scientific and policy institutions that potentially complicate pain-related patient outcomes (Meghani & Vapiwala, 2018).

Despite much debate, analgesics – and opioids in particular - remain central to the management of moderate to severe cancer-related pain (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; World Health Organization [WHO], 2018). Although pain management guidelines assist in clarifying the salience of analgesic use for clinicians, there continues to be a critical paucity of empirical data exploring the trade-offs employed by patients in their decisions to use analgesics for cancer pain. This knowledge deficit is critical to address, given the high rates of analgesic nonadherence

for cancer pain identified in previous studies (Meghani et al., 2014; Meghani & Knafl, 2017; Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2017; Rhee, Kim, & Kim, 2012). Inconsistent analgesic use for cancer pain has been noted as both a strong predictor of increased healthcare resource utilization (Meghani & Knafl, 2016) and a predictor of poor pain-related and associated quality of life outcomes (Manzano, Ziegler, & Bennett, 2014).

In response to both the documented need for individualized pain treatment and notable literature gap regarding patient heuristics, this study uses an innovative analytical technique - maximum difference (MaxDiff) scaling - to elicit the analgesic trade-offs patients with cancer employ based on their pain management beliefs. Although MaxDiff has traditionally been used to identify consumer preferences among brands or items, it has become an attractive technique to elicit importance scores, also known as *utilities*, in relation to phenomena within the social sciences domains (Feudtner et al., 2015; J.J. Louviere, Flynn, & Marley, 2015; Mooney-Doyle, Deatrick, Ulrich, Meghani, & Feudtner, 2018; October, Fisher, Feudtner, & Hinds, 2014). In other words, individuals' trade-offs reflect desirability of a given choice, thereby reflecting the amount of value the individual derives from that choice.

Prior investigations have used trade-off analysis techniques, such as choice-based-conjoint analysis, to identify analgesic treatment utilities (e.g. trade-offs between type of analgesic, side-effects type, side-effect severity, % pain relief from using analgesics, and out-of-pocket cost of analgesics) among cancer outpatients and minority subgroups (Meghani, Chittams, Hanlon, & Curry, 2013; Meghani & Knafl, 2017). However, to our

knowledge, this is the first study to understand the role of analgesic beliefs in these trade-offs. Using MaxDiff analysis, the specific aims of this study are to: (1) identify patient trade-offs based on analgesic treatment beliefs; (2) rank and describe the utilities prioritized by patients using a MaxDiff-derived *k* means cluster analysis; and (3) describe the clusters in terms of key sociodemographic and clinical variables. Thus, these authors seek to determine patients' trade-off on analgesic treatment beliefs, rank each belief according to the perceived value assigned by the participants, identify if there are any unique clusters based on participants' ranking of each belief, and describe the identified clusters based on participants' sociodemographic and clinical characteristics.

Methods

Sample and Setting

This is a secondary analysis of an existing dataset (NIH/NINR RC1-NR011591: PI Meghani, S.H.; (Meghani et al., 2015). The parent study used a three-month prospective observational design with repeated measures (baseline, T1 and 3-month follow-up, T2). The primary aim of the parent study was to identify cancer pain management and analgesic adherence disparities between African-American and White patients. Convenience sampling was used to recruit from two outpatient medical oncology services at the Hospital of the University of Pennsylvania, Philadelphia, PA between December 2009 and August 2011. Approval for the parent study was obtained from the University of Pennsylvania Institutional Review Board (IRB) and all patients provided written informed consent.

Inclusion criteria consisted of patients 18 years or older who self-identified as White or African-American, were diagnosed with solid tumor or multiple myeloma, reported cancer pain, and had at least one prescription of oral around-the-clock analgesic. Patients receiving pain control through a transdermal system were excluded.

A sample of 241 subjects agreed to participate in the parent study. There was an estimated 14% attrition rate between T1 and T2 and 207 subjects completed the study (participant recruitment flow diagram published previously in Meghani et al. (2015). Of note, there was no disproportionate attrition by race or health status in the parent study. For the purpose of this analysis, data are used for the 207 subjects who completed the parent study at T2.

The current study was deemed exempt by the University of Pennsylvania IRB as all data were previously de-identified of protected health information and, therefore, does not meet the definition of human subjects research.

Measures

Analgesic beliefs and barriers: The Barriers Questionnaire-II (BQ-II) (Ward et al., 1993), a 27-item self-report instrument, was used to evaluate how patients' beliefs function as barriers to optimal cancer pain management (internal consistency reliability=0.89). The BQ-II evaluates pain management concerns across eight domains, including fears of analgesic addiction, tolerance, or side effects; cancer pain fatalism; a desire to be a 'good patient'; fears that pain will distract the health provider from focusing on cancer treatment or that analgesics will harm the immune system; and concern that analgesics mask underlying illness processes.

Analgesic side-effects: The Medication Side-Effects Checklist (MSEC) was used to assess the presence and severity of analgesic side-effects (internal consistency reliability=0.80) (Ward, Carlson-Dakes, Hughes, Kwekkeboom, & Donovan, 1998). The MSEC identifies eight common side-effects related to analgesic use: constipation, drowsiness, nausea, vomiting, confusion, dry mouth, stomach irritation, and itching. Presence of side effects is elicited with a numerical scale, 0-8; severity of side-effects is measured with a numerical scale, 8-80 (from 'not severe' to 'extreme severity').

Pain severity and pain-related function: Pain severity was assessed using the Brief Pain Inventory (BPI). The two subscales of the BPI include a 4-item pain intensity measure and a 7-item pain-related functional interference score (based on general activity, mood, walking ability, normal work, relationships, sleep, and life enjoyment) (Cleeland & Ryan, 1994). Items are scored on a 0-10 scale (no pain – pain as bad as you can imagine; no interference – worst possible interference). The BPI maintains a Cronbach's alpha ranging from 0.77 to 0.91 in its use among cancer patients (Anderson et al., 2002; Cleeland et al., 1994).

Pain Management Index: Based on the WHO's cancer pain management guidelines (1986, 1996, 2018), Pain Management Index (PMI) is frequently used to measure the adequacy of analgesic treatment in cancer patients. PMI offers a comparative score of the most potent analgesic used in relation to the patient's reported pain. PMI is calculated by taking the most potent analgesia used according to the WHO's 3-step cancer pain analgesic ladder and subtracting the patient's worst pain BPI score. A

negative PMI implies inadequate analgesic prescription strength given reported pain level.

Social support questionnaire: Subjects' level of social support and satisfaction with perceived social support was elicited using a 6-item instrument (an abbreviated version of the 27-item Social Support Questionnaire) (Sarason, Levine, Basham, & Sarason, 1983). There are two parts to the question: first, subjects list the individuals in their life who provide social support and, second, they provide their satisfaction level with the support.

Prescribed analgesics: Prescribed analgesics were classified per the WHO (1986, 1996, 2018) cancer pain analgesic ladder. Categories include step 1 (nonopioids, e.g. nonsteroidal anti-inflammatories), step 2 (weak opioids, e.g., tramadol, codeine), and step 3 (strong opioids, e.g., methadone, oxycodone, morphine).

Sociodemographic and clinical variables: Self-reported sociodemographic data collected were age, gender, self-identified race, marital status, education, health insurance, household income, and job status. Clinical variables including stage of cancer, time since cancer diagnosis, past history of alcohol or substance abuse, history of depression, and comorbidities were gathered from the patient's medical record and used to calculate a Charlson Comorbidity Score (Charlson, Pompei, Ales, & MacKenzie, 1987). Patients rated their general health on a five-point likert scale (from poor to excellent) and then indicated the number of days in the prior 30-day period in which they would rate their physical and mental health as "not good". Pain and treatment related variables included: the duration of cancer pain and the type and numbers of prescribed

analgesics and coanalgesics used. Coanalgesics refer to medications used in conjunction with analgesics to optimize pain control, such as antidepressants, benzodiazepines, or neuropathic agents.

Statistical Analysis

MaxDiff analysis was completed using JMP® Pro 14 software. Descriptive statistics were computed on Stata/IC 15. First, descriptive statistics were generated for sociodemographic and clinical variables (e.g., means and standard deviations for continuous variables, frequencies and percentages for categorical variables).

Trade-Offs Based on Analgesic Beliefs

Trade-offs for the sample (N=207) were derived using a MaxDiff analysis. MaxDiff is a trade-off methodology derived from Random Utility Theory (Thurstone, 1927). MaxDiff maintains noted measurement advantages over traditional survey techniques, other ranking methods and some discrete choice analyses methods, which may confuse participants with too many options in a given choice set and/or muddle findings by lacking clear measurement differences between choices (Louviere, Flynn, & Carson, 2010; Marley & Flynn, 2015). Ultimately, MaxDiff allows for (1) increased discrimination through forced tradeoffs among items and between subjects' responses on the given items; (2) demonstrates optimal ease of use for respondents from diverse education and cultural backgrounds; and (3) avoids scale use bias by requiring respondents to make choices rather than merely rating the strength of their preferences (Sawtooth Software, 2019).

MaxDiff requires subjects to identify both the 'best' and 'least desirable' option available within a given set of choices (Finn & Louviere, 1992; Marley & Louviere, 2005). Thus, it is also referred to as 'best-worst scaling' and identifies the 'maximum difference' in preference between the 'best' and 'worst' choices available (Marley & Flynn, 2015). Subjects in this current study selected the belief statement, also known as an *attribute*, that was "most" and "least" important in thinking about his or her pain medications. Responses allowed us to calculate the maximum difference between patient responses across eight distinct choice sets. The barriers elicited were based on the validated Barriers Questionnaire-II (Ward et al., 1993). Table 1 lists the BQ-II domains (Ward et al., 1993). Abbreviated statements used to represent each of the questionnaire attributes in the following sections are also provided in Table 1.

MaxDiff analysis results provided measures of marginal probability, which estimate the probability that a patient conveys a preference for the corresponding attribute over other listed attributes (SAS Institute, 2019). The marginal probabilities of all attributes sum to 1.00. MaxDiff analysis also captures measures of marginal utility, which indicate the perceived value of the corresponding attribute; hence, a larger utility suggests greater corresponding value to the patient (SAS Institute, 2019). The marginal utilities provide both positive and negative values and sum to 0. A chi-square likelihood ratio test was calculated as a part of this initial MaxDiff analysis to elicit whether patients' analgesic beliefs were independent of their choices related to pain medications ($p \leq 0.05$).

Unique Clusters Based on Analgesic Beliefs

MaxDiff-derived utilities were subjected to a *k-means* cluster analysis. *K means* is a prototype-based clustering technique that applies one-level of partitioning using an unsupervised learning algorithm (Kaufman & Rousseeuw, 1990). *K means* produces non-overlapping clusters, such that each data object is assigned to one cluster. This technique is preferred for this study since hierarchical or fuzzy clustering techniques would use nested or overlapping cluster membership that would complicate the process of identifying clear utility trade-offs (Tan, Steinbach, Karpatne, & Kumar, 2019).

A goal with the *k means* clustering analysis algorithm is to find groups in the data with a pre-specified number of *k* centroids (Hastie, Tibshirani, & Friedman, 2009). Data is then assigned to its closest centroid using a Euclidean distance minimization equation. Next, centroids are recomputed in an iterative process until they show no further signs of change (Tan et al., 2019). The goal of clustering was to identify similarities among groups of individuals in how they prioritize their beliefs related to analgesic treatment. We selected a 2-cluster model a priori for analysis. Two clusters provided a cubic clustering criterion (CCC) of -1.95. A lower CCC represents a minimal within-cluster sum of squares (Tan et al., 2019). An ad hoc quality check confirmed smaller CCCs of -2.31 and -2.18 for 3- and 4-cluster models respectively. A 5-cluster model provided the largest CCC at -0.24, however, for both parsimony and clarity, as well as the sample size, 2 clusters were used.

Finally, MaxDiff utility rankings were calculated for each cluster using the MaxDiff analysis process, as described above (Sawtooth Software, 2013). These rankings sum to 100.

Cluster Description by Sociodemographic and Clinical Variables

Once clusters were identified and ranking completed, key sociodemographic and clinical variables were then recalculated for each cluster and statistical tests were used to identify significant differences between them used Stata/IC 15 (e.g., *t*-tests for continuous variables and chi-square for categorical variables).

Results

On average, the subjects were 53.8 years (SD=11.1). The majority self-identified as White (58.5%), female (56.5%), and were college/trade-school educated (48.8%) or higher (15.9%) (Table 2). The vast majority of patients were diagnosed with a solid tumor and less than one-fifth had multiple myeloma. Just under one-third of patients had Stage IV cancer and more than half rated their general health as "fair" or "poor" in the 30 days preceding data collection. Most patients were prescribed a strong (WHO step 3) opioid, classified as WHO step 3. In the week prior to the survey, on average patients reported a "worst pain" score of 6.9 on a 0-10 scale and reported about four different analgesic side effects.

Trade-Offs Based on Analgesic Beliefs

MaxDiff analysis results for the sample (N=207) include marginal utilities and marginal probabilities for each of the questionnaire attributes (Figure 1). MaxDiff likelihood ratio testing suggests that patient beliefs (as represented by the survey

attributes) are a significant factor in their choices when thinking about pain medicines (chi-square = 498.145, $p < .0001$).

'Knowing body' and 'Immune system' yielded the highest marginal probabilities. In essence, patients are 23.9% more likely to make trade-offs about analgesic medications based on 'Knowing body' than other competing beliefs. Similarly, 'Knowing body' had a marginal utility of 95.7%, meaning this belief was about twice as important to patients than 'Immune system' or 'Need it later', and more than four times as important in making trade-offs than 'Addicted to meds'. Not only do patients with cancer identify 'Knowing body' as the most important belief but they are also more likely to make choices based on it when compared to other beliefs.

Four attributes on the questionnaire yielded negative marginal utilities scores, indicating no or limited perceived value of these beliefs in relation to pain medicines. These utilities included, 'Doctors won't focus on cancer', 'Be strong'; and 'Say embarrassing things'. The utility of 'Complainer' was minimal at best and could not be measured using the data platform. Ultimately, patients are markedly less likely to trade-off based on these four utilities than the beliefs reflected by the other survey attributes.

Utility Ranking: MaxDiff-Derived Cluster Analysis

Using methods described previously, a 2-cluster model was selected. The parallel coordinate plot (Figure 2) displays the structure of the cluster observation means and illustrates more explicitly how cluster outcomes differ (discussed in more detail by cluster). Both clusters ranked 'Knowing body' as the most salient utility (Table 3);

supporting the trade-off findings previously discussed that this belief tends to be the most important for patients with cancer.

For cluster 1, 'Side effects' was ranked as 2nd most important. The least relevant utilities, ranked 9th and 10th respectively, were 'Say embarrassing things' and 'Won't focus on cancer'. This further strengthens the argument that these utilities have little or no perceived value and are, ultimately, of nominal importance in decisions related to pain medication. There were some differences noted in cluster 2 rankings. The 'Need it later' utility was ranked 2nd among cluster 2 members. Bottom ranked utilities reflected beliefs related to 'Complainer' (9th) and 'Say embarrassing things' (10th),

'Addicted to meds' was ranked fourth by both clusters, connoting a moderate level of importance for all patients in the sample. The prioritizing of 'Addicted to meds' in the top 50% of utilities by both clusters demonstrates a moderately high belief in addiction across the sample. While not the most or even the second most important utility, addiction to analgesics is a consistently relevant factor surrounding pain treatment beliefs.

Overall, the clusters shared over 50% of the top five ranked utilities in common, as well as over half of their bottom five (Table 3). These results show that the prioritization of patient beliefs still varies significantly between clusters, demonstrating broader substantive differences among how cancer patients' beliefs inform their thoughts about analgesic use. This variation reflects the differences in individual beliefs and the weight given those beliefs when it comes to analgesic use.

Cluster Description in Terms of Sociodemographic and Clinical Variables

Table 4 shows sociodemographic and clinical variables by cluster. Less than half of cluster 1 (n=53) self-identified as African-American (43.4%) and the majority were female (60.4%). This group rated their "worst pain" as slightly more severe than cluster 2. Additionally, cluster 1 patients endorsed a significantly higher severity related to analgesic side effects than cluster 2 ($p = 0.043$). On average, cluster 1 patients were prescribed roughly two analgesic medications to alleviate their cancer pain, the majority of which were a strong opioid (WHO step 3). They also reported experiencing about four different analgesic side effects. The majority of cluster 2 (n=154) self-identified as White (59.1%) and female (55.2%) (Table 4). The number of analgesics (including strong opioids) prescribed and the number of side effects experienced were very similar to cluster 1. Patients in cluster 1 and cluster 2 did not vary significantly in age, gender, race, or other sociodemographic variables (Table 4). Other clinical variables included in the analysis showed no statistically significant differences.

Discussion

In our study, we first sought to identify patient trade-offs based on analgesic treatment beliefs using a MaxDiff analysis. We subsequently ranked the utilities prioritized by patients using a *k* means cluster analysis and then described the clusters in terms of key sociodemographic and clinical variables. To our knowledge, this is the first study to use the MaxDiff methodology in this context. Previous studies have noted that patients with cancer pain stop taking their analgesics for a number of reasons. Some of these include the severity of side effects (Manzano et al., 2014; Meghani & Bruner, 2013;

Meghani et al., 2015); concern regarding the physiological consequences of opioid use, such as dependence or addiction (Jacobsen et al., 2014; Simone, Vapiwala, Hampshire, & Metz, 2012); a firm conviction that clinicians should focus on treating the cancer rather than pain (Rhee et al., 2012); and the hesitancy of patients' family and caregivers to use analgesics (Lee et al., 2015; Schumacher et al., 2014). Our analysis suggests that patient trade-offs based on certain beliefs about cancer pain management yield a significant influence in their choices about analgesic use. This finding is consistent with previously demonstrated empirical links between analgesic beliefs and analgesic nonadherence behaviors (Liang et al., 2013; Meghani & Bruner, 2013; Torresan et al., 2015; Valeberg, Miaskowski, Paul, & Rustoen, 2016). Despite these study findings, we still know little about how patients make the decision to use analgesics based on their beliefs.

A striking result was that the belief, 'Many people with cancer get addicted to meds', was not a top priority for participants. In fact, this utility was ranked 4th and found to be of only moderate importance among both clusters. One may have anticipated a higher importance score related to addiction beliefs given these data were collected at the height of the opioid addiction epidemic. Despite some studies that suggest a worry about dependence or addiction to opioids as significant in the patient decision-making process (Jacobsen et al., 2014; Liang et al., 2013; Simone et al., 2012), researchers have argued that addiction concerns do not explain objective analgesic adherence in the cancer pain population (Meghani et al., 2015). In addition, this finding is consistent with other evidence showing that although a significant number of patients express some concern

about addiction to opioids, this belief is also not correlated with subjective measures of adherence (Rhee et al., 2012).

Participants across the sample consistently prioritized the 'Pain meds keep you from knowing what is going on in your body' utility with the highest level of importance. This result validates the emphasis patients place on knowing their own bodies ('Knowing body') in thinking about their pain medications. Furthermore, this belief may yield more significant trade-off power over other beliefs and may directly correlate with a patients' likelihood to use analgesics to mitigate their cancer pain burden. Future research should examine these issues. This finding of knowing one's body emphasizes how important it is to cancer patients to have a firm understanding of their underlying physiological processes.

The high relevance of knowing one's body validates the results of several previous empirical studies. Investigators found that cancer patients with higher rates of intentional analgesic nonadherence were more likely to agree with the 'Knowing body' statement (Meghani & Bruner, 2013). In a recent survey of patients with different cancers, the presence of pain was significantly linked to the status of disease (Rau et al., 2017), which may explain how patients use pain to better understand their bodies and why they stop taking analgesics accordingly. Other findings suggest that some patients deny pain as a symptom of disease, which may increase barriers to analgesic utilization (Torresan et al., 2015). Another study by Liang and colleagues (2013) showed that about one-third of patients believe opioids should only be used late in the disease process,

consistent evidence that analgesics may become more acceptable once patients feel they have a clearer understanding of what is going on in their bodies.

Consistent with previous research that associates increased side effects and side effects severity with decreased analgesic adherence (Manzano et al., 2014; Meghani & Bruner, 2013; Meghani et al., 2014), our cluster analysis findings highlights the importance of addressing patients' side effects when using analgesics for cancer pain. In addition, the severity of side effects also differed significantly between cluster 1 and cluster 2, further suggesting that the utility of 'Side effects' may be a salient concern for some and not others. For example, an earlier study involving this sample concluded that more than a quarter of patients were found to make trade-offs based on multiple concerns, including both type and the severity of side effects (Meghani & Knafl, 2017).

'If you use pain medicine now, it won't work when you need it later' was ranked among the top two utilities for cluster 2. In other words, a worry about tolerance to analgesics may be a likely concern for patients with cancer pain. This utility is informed by the belief that if patients with cancer pain take analgesics whenever they need it, then those same medications will not be effective when the pain increases in severity and the need for relief is more substantial. This correlates with a study that showed a majority of patients agree that using an opioid in earlier disease stages will prevent its optimal effect later (Liang et al., 2013). Some trade-offs, such as 'Won't focus on cancer', 'Be strong'; 'Say embarrassing things'; and 'Complainer', were found to have low utility. These findings are in alignment with a previous study showing that these beliefs tend to have

less importance among patients with cancer pain than ‘Knowing body’ or ‘Immune system’ (Valeberg et al., 2016).

Clinical Implications

A number of relevant clinical implications are suggested. First, clinicians who prescribe and administer analgesics to treat cancer pain should elicit patients’ analgesic beliefs in order to ensure safe use and minimize adverse outcomes. The analgesic treatment priorities and beliefs of patients may not always be aligned with the priorities of clinicians, such as the case with addiction concerns. Second, analgesic regimens should be determined in partnership with patients to ensure patients’ beliefs are optimally considered in creating prescription pain treatment plans. Prescribing in partnership requires the integration of patient-centered care with evidence-based pain guidelines, which are currently severely lacking, specially for opioid pain management for cancer pain (Meghani & Vapiwala, 2018). Third, optimizing nonopioids and weak opioids that cause fewer adverse effects per the WHO (1986, 1996) cancer pain ladder may address patients’ beliefs. However, it must be emphasized that many guidelines continue to suggest the use of strong opioids in the treatment of moderate to severe cancer pain (NCCN, 2019; Paice et al., 2016; WHO, 2018). Fourth, our findings support well-cited recommendations in academia and policy calling for tailored patient education related to opioid use, risks, and benefits (Christie et al., 2017; National Academies of Sciences, 2017; National Academy of Medicine, 2017; Oldenmenger et al., 2018). As future research elucidates the link between individual beliefs and actual analgesic taking behaviors, interventions related to analgesic prescribing and education should aim to

become more patient-centric. It is imperative that the relationship between beliefs and analgesic adherence be further clarified for the sake of improved patient safety and health outcomes, particularly in the current sociopolitical milieu of the opioid addiction epidemic.

Limitations

There were several limitations to consider. First, the data was collected between 2009 and 2011; this time period, however, overlapped with the second wave of the opioid crisis (Centers for Disease Control & Prevention, 2018), making the findings highly relevant to the current sociopolitical milieu. Second, the sample is limited to patients who self-identify as either African-American or White, excluding the utilities of patients from other diverse backgrounds. Additional studies might examine if differences exist among other ethnic, racial, and minority populations. Third, the parent study questionnaire provided patients with ten attribute statements assessed through eight different choice sets. There are a broad variety of attributes that were likely not included in our study. In the future, researchers may consider a more extensive attribute list, as well as the integration of qualitative methods to validate findings and cultivate a deeper understanding of this phenomenon. Finally, provider-, family-, and system-level factors and their influence on analgesic use were not accounted for in the MaxDiff analysis. Ongoing investigations might combine family and provider factors along with patient utilities to describe differences in trade-offs, as well as the link to analgesic taking behaviors.

Conclusion

There is much yet to be explored about how beliefs and resultant utilities factor into analgesic use and overall adherence in the management of cancer pain. In better understanding the trade-offs made by patients, prescribers have improved opportunity to tailor pain treatment strategies to individual needs. The current climate of the opioid crisis and its broad implications in practice, policy, and research require investigators and clinicians to cultivate a deeper understanding of how patients' beliefs inform their decision-making processes around analgesic taking behaviors.

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Table 1. Attributes for MaxDiff Analysis with Abbreviations Based on Barriers Questionnaire-II (BQ-II) Domains.

BQ-II Domains (Ward et al., 1993)	**Attributes for MaxDiff Analysis**	**Abbreviated Attribute Statement**
1. Fear of addiction.	▪ Many people with cancer get addicted to pain meds.	▪ Addicted to meds
2. Fear of tolerance.	▪ If you use pain medicine now, it won't work when you need it later.	▪ Need it later
3. Fear of side effects.	▪ It is easier to deal with the pain than the side effects that come from the pain meds.	▪ Side effects
	▪ Pain meds make you say or do embarrassing things.	▪ Say embarrassing things
4. Fatalism about cancer pain.	▪ Cancer pain cannot be relieved with medications.	▪ Cannot be relieved
5. Desire to be a good patient.	▪ If I talk about pain, people will think I'm a complainer.	▪ Complainer
	▪ It is important to be strong by not talking about pain.	▪ Be strong
6. Fear of distracting health provider from treating cancer.	▪ If doctors have to concentrate on pain they won't focus on treating the cancer.	▪ Won't focus on cancer
7. Fear that analgesics impair the immune system.	▪ Pain meds weaken the immune system.	▪ Harm immune system
8. Concern that analgesics may mask ability to monitor illness symptoms.	▪ Pain meds keep you from knowing what is going on in your body.	▪ Knowing body

Table 2. Relevant Sociodemographic, Illness, and Pain-Related Characteristics (n=207).

Variable	Range	*n*(%)[1]	Mean (SD)
Age	23-75		53.8 (11.1)
Gender	Male	90 (43.5)	
	Female	117 (56.5)	
Self-identified race	African-American	86 (41.5)	
	White	121 (58.5)	
Education	Elementary	3 (1.5)	
	High School	70 (33.8)	
	College/Trade school	101 (48.8)	
	More than college	33 (15.9)	
Household income	< 30,000	73 (35.3)	
	30,000-50,000	36 (17.4)	
	50,000-70,000	37 (17.9)	
	70,000-90,000	24 (11.6)	
	>90,000	37 (17.9)	
Job status	Full-time outside home	43 (20.8)	
	Part-time outside home	12 (5.8)	
	Full-time at home	4 (1.9)	
	Part-time at home	4 (1.8)	
	Retired	44 (21.3)	
	Unemployed	25 (12.1)	
	Other	75 (36.2)	
Primary Insurance[2]	Private	107 (51.9)	
	Medicare	41 (19.9)	
	Medicaid	27 (13.1)	

	Multiple Other	25 (12.1) 6 (2.9)	
Health literacy	3-15		13.1 (2.6)
Social support	0.17-9.00		3.7 (2.1)
Cancer type	Lung Breast Gastrointestinal Genitourinary/reproductive Multiple myeloma Other solid tumors	32 (15.5) 38 (18.4) 31 (15.0) 25 (12.1) 34 (16.4) 47 (22.7)	
Cancer stage	I II III IV Unknown or unsure	20 (9.7) 33 (15.9) 37 (17.9) 64 (30.9) 53 (25.6)	
Time since cancer diagnosis	1-120 months		36.7 (35.5)
Charlson comorbidity index	0-13		4.3 (2.6)
General health	Excellent Very good Good Fair Poor	9 (4.3) 23 (11.1) 63 (30.4) 77 (37.2) 35 (16.9)	
Physical health not good (within past 30 days)	0-30		14.7 (10.7)
Mental health not good (within past 30 days)	0-30		9.5 (10.7)

History of substance abuse	Yes No	35 (16.9) 172 (83.1)	
Presence of depression	Yes No	87 (42.0) 120 (58.0)	
Index analgesic	WHO Step 1 WHO Step 2 WHO Step 3	19 (9.2) 22 (10.6) 166 (80.2)	
Average pain (last week)	0-10 (no pain - pain as bad as you can imagine)		4.9 (2.1)
Pain-related functional interference score	7-70 (does not interfere - interferes completely)		35.2 (15.9)
Pain Management Index	-2 -1 0 1 2 3	5 (2.4) 13 (6.3) 92 (44.4) 63 (30.4) 31 (15.0) 3 (1.4)	
Barriers Questionnaire (BQ-II)	0-135		66.8 (20)
Number of analgesic side-effects (MSEC)	0-8		3.8 (2.4)
Severity of analgesic side-effects (MSEC)	8-80 (not severe – extremely severe)		25.2 (15.0)

[1]No missing values unless otherwise noted. SD: Standard deviation.

[2]One value missing.

Table 3. MaxDiff Utilities Ranked by Cluster

Cluster 1 (n=53) Mean (SD)		**Cluster Rank Order**	**Cluster 2 (n=154) Mean (SD)**	
Knowing body	14.204 (6.266)	1	Knowing body	17.388 (6.699)
Side effects	13.899 (5.573)	2	Need it later	15.015 (7.415)
Be strong	12.353 (7.603)	3	Harm immune system	14.137 (6.568)
Addicted to meds	11.949 (9.015)	4	Addicted to meds	13.560 (9.040)
Need it later	11.380 (6.415)	5	Cannot be relieved	11.907 (6.382)
Complainer	10.045 (7.569)	6	Won't focus on cancer	9.838 (8.198)
Harm immune system	8.254 (5.751)	7	Side effects	9.830 (4.730)
Cannot be relieved	6.579 (5.466)	8	Be strong	4.333 (4.202)
Say embarrassing things	6.344 (5.687)	9	Complainer	2.066 (3.064)
Won't focus on cancer	4.993 (5.286)	10	Say embarrassing things	1.927 (1.959)

*The middle column provides a rank order numbered 1-10. The two left-hand columns provide the order of cluster 1 utilities based on rescaled MaxDiff probabilities. Similarly, the two right-hand columns provide the order of cluster 2 utilities.

Table 4. Key Clinical Variables by Cluster.

Variable	Cluster 1 (n=53)	Cluster 2 (n=154)	P-value[a]*
Mean (SD)			
Age (years)	54.2 (12.5)	53.7 (10.7)	0.798
Duration of disease (months)	30.5 (29.4)	38.9 (37.2)	0.138
Charlson Comorbidity Score (0-13)	4.4 (2.3)	4.3 (2.8)	0.725
Social Support Amount (0.17-9.00)	4.1 (2.3)	3.6 (2.0)	0.102
General health not good (number of days within last 30 d)	3.5 (1.0)	3.5 (1.1)	0.862
Physical health not good (number of days within last 30 d)	15.7 (11.3)	14.4 (10.5)	0.439
Mental health not good (number of days within last 30 days)	8.3 (10.1)	9.9 (10.9)	0.333
Pain Management Index (-2 - +3)	0.5 (0.8)	0.6 (1.0)	0.687
Number of analgesics (excluding coanalgesics) WHO Step 1	0.3 (0.5)	0.2 (0.4)	0.410
Number of analgesics (excluding coanalgesics) WHO Step 2	0.2 (0.4)	0.3 (0.6)	0.087
Number of analgesics (excluding coanalgesics) WHO Step 3	1.7 (1.0)	1.5 (0.8)	0.099
Total number of analgesics prescribed (excluding coanalgesics)	2.2 (1.0)	2.0 (0.8)	0.309
Worst pain (0-10)	7.1 (2.0)	6.8 (2.5)	0.530
Number of analgesic side effects (MSEC, 0-8)	4.1 (2.4)	3.7 (2.5)	0.266

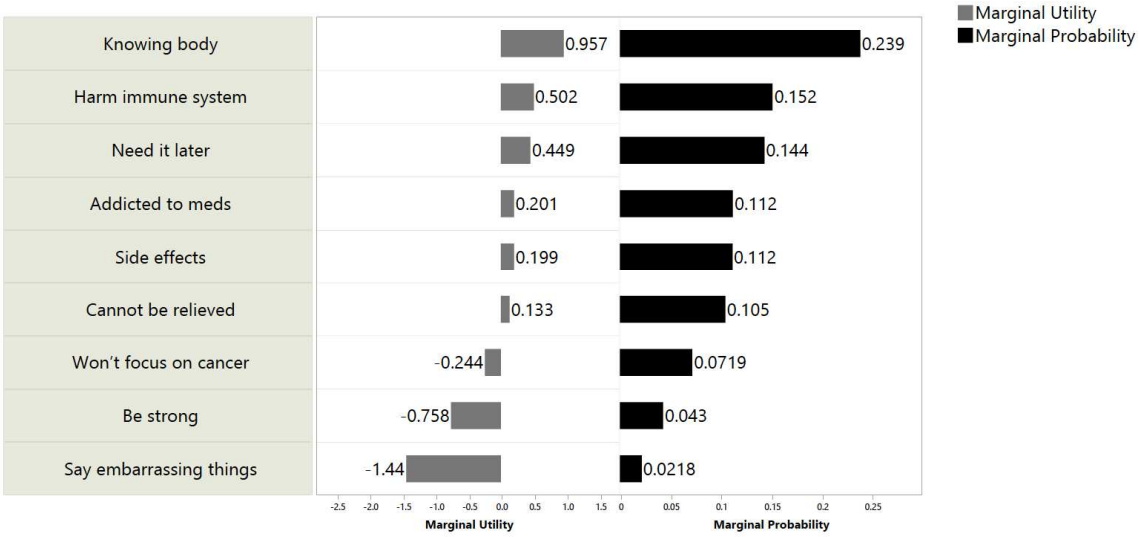
Severity of side effects (MSEC, 0-80)	28.8 (15.6)	24 (14.6)	0.043
Health literacy (3-15)	13.3 (2.7)	13.0 (2.6)	0.413
Barriers Questionnaire-II (BQ-II, 0-135)	63.7 (19.4)	67.8 (20.2)	0.200
Frequency (%)			
Race			0.751
African-American	23 (43.4)	63 (40.9)	
White	30 (56.6)	91 (59.1)	
Gender			0.512
Male	21 (39.6)	69 (44.8)	
Female	32 (60.4)	85 (55.2)	
Marital Status			0.397
Married	25 (47.2)	85 (55.2)	
Separated	5 (9.4)	11 (7.1)	
Divorced	10 (18.9)	22 (14.3)	
Widowed	4 (7.5)	4 (2.6)	
Never married	9 (17.0)	32 (20.8)	
Education			0.922
Elementary	1 (1.9)	2 (1.3)	
High school	16 (30.2)	54 (35.1)	
College/trade school	27 (50.9)	74 (48.1)	
More than college	9 (17.0)	24 (15.6)	
Household income			0.861
< 30,000	21 (39.6)	52 (33.8)	
30,000-50,000	9 (17.0)	27 (17.5)	

50,000-70,000	7 (13.2)	30 (19.5)	
70,000-90,000	6 (11.3)	18 (11.7)	
>90,000	10 (18.9)	27 (17.5)	
Primary insurance			0.731
Private	25 (47.2)	82 (53.6)	
Medicare	13 (24.5)	28 (18.3)	
Medicaid	6 (11.3)	21 (13.7)	
Multiple	1 (1.9)	5 (3.3)	
Other	8 (15.1)	17 (11.1)	
Job status			0.934
Full-time outside home	11 (20.8)	32 (20.8)	
Part-time outside home	4 (7.5)	8 (5.2)	
Full-time at home	1 (1.9)	3 (1.9)	
Part-time at home	0 (0)	4 (2.6)	
Retired	11 (20.8)	33 (21.4)	
Unemployed	6 (11.3)	19 (12.3)	
Other	20 (37.7)	55 (35.7)	
Cancer stage			0.721
I	2 (3.8)	11 (7.1)	
II	7 (13.2)	17 (11.0)	
III	6 (11.3)	25 (16.2)	
IV	17 (32.1)	43 (27.9)	
Unknown or unsure	21 (39.6)	58 (37.7)	
			0.541
	9 (17.0)	23 (14.9)	

Cancer type	12 (22.6)	26 (16.9)	
Lung	9 (17.0)	22 (14.3)	
Breast	4 (7.5)	21 (13.6)	
Gastrointestinal	7 (13.2)	27 (17.5)	
Genitourinary/reproductive	12 (22.6)	36 (22.7)	
Multiple myeloma			
Other solid tumors			
History of substance abuse			0.659
Yes	10 (18.9)	25 (16.2)	
No	43 (81.1)	129 (83.8)	

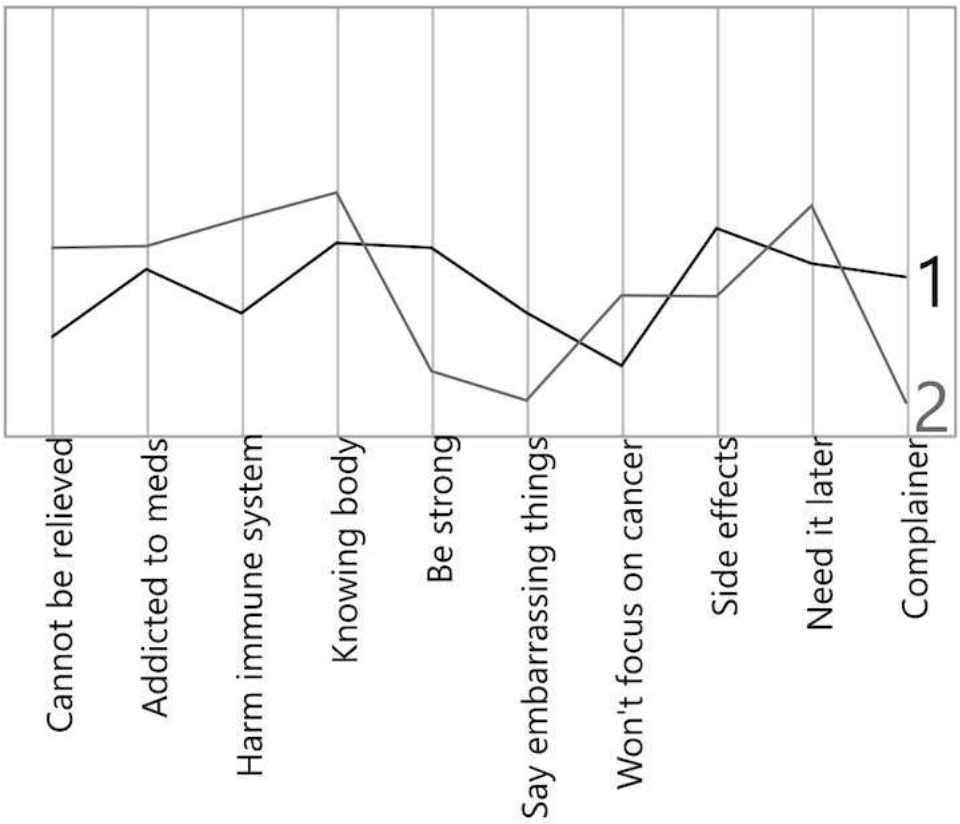
*p-values are based on t-tests for continuous variables; chi-squared for categorical variables.

Figure 1. MaxDiff Marginal Utility and Marginal Probability.



*Attributes are listed in descending order by marginal utility (left) and marginal probability (right).

Figure 2. Parallel Coordinate Plot: MaxDiff Cluster Means.



*Observation means of rescaled marginal probabilities by cluster. This plot presents utilities by cluster membership and is a visual representation of the data found in Table 3.

CHAPTER 4

The Association Between Analgesic Treatment Belief Clusters and Electronically-Monitored Analgesic Adherence for Cancer Pain

ABSTRACT

Objectives: To determine if clusters based on cancer patients' analgesic treatment beliefs predicted objective analgesic adherence as measured by an electronic medication monitoring system while accounting for relevant confounders.

Sample and Setting: The sample (N=207) consisted of outpatient oncology patients, ≥ 18 years, self-identified as White or African-American, diagnosed with solid tumor or multiple myeloma, and prescribed at least one around-the-clock analgesic prescription for reported cancer pain.

Methods and Variables: This is a secondary analysis of an existing dataset. We applied general linear modeling with a backward elimination approach to determine if previously identified analgesic treatment belief clusters were associated with adherence behaviors.

Results: Significant explanatory factors were experiential in nature and included sociodemographic, clinical, and pain-related variables ($p < 0.05$), explaining 21% of the variance in analgesic adherence. Analgesic belief clusters were not predictive of adherence.

Implications for Nursing: Future research should examine sociodemographic and other clinical factors, as well as the influence of analgesic treatment beliefs, to better understand analgesic adherence behaviors.

Knowledge Translation: Oncology nurses should address the experiential factors affecting analgesic adherence, become aware of evolving pain management strategies

amid the opioid epidemic, and understand how the notion of ‘adherence’ may change given increased emphasis on ‘as-needed’ analgesic relief for cancer pain.

The Association Between Analgesic Treatment Belief Clusters and Electronically-Monitored Analgesic Adherence for Cancer Pain

The majority of patients with cancer report pain and as many as 38% report their pain as moderate to severe (Shi et al., 2011; van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016). Although there is a lack of data on outcomes related to long-term opioid use for cancer pain (Meghani & Vapiwala, 2018), a number of cancer pain guidelines continue to identify opioids as a core component of moderate to severe cancer pain management (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; World Health Organization [WHO], 2018). While some pain management guidelines promote the use of complementary and alternative strategies (Dowell, Haegerich, & Chou, 2016; NCCN, 2019), their affordability may be unmanageable for some and several systematic reviews have noted insufficient evidence to support their clinical efficacy in alleviating cancer pain (Hetkamp et al., 2019; Kim, Loring, & Kwekkeboom, 2018; Kim, Kang, & Lee, 2018; Shin et al., 2016; Wayne et al., 2018). Thus, analgesic use - and opioid use in particular - remains a primary modality for achieving moderate to severe pain control in the cancer population. Although there are a number of national initiatives underway that focus on advancing pain science from the provider perspective (National Academies of Sciences, 2017, 2020; National Academy of Medicine, 2017), we still know little about the predictors of patients' actual analgesic taking behaviors.

Given the opioid epidemic and its healthcare implications, the phenomenon of analgesic adherence requires better understanding. Patients who experience less pain

relief with analgesic use or higher side effect severity are typically less adherent to prescribed analgesic regimens, whereas those prescribed a strong opioid (classified as WHO step 3) or a long-acting opioid show higher levels of adherence (Meghani, Thompson, Chittams, Bruner, & Riegel, 2015). Patient beliefs have been shown to predict adherence behaviors. For example, patients who believed their doctor should focus on curing illness over treating pain demonstrated increased adherence behaviors. Inconsistent analgesic adherence for cancer pain has been correlated with increased hospitalization rates (Meghani & Knafl, 2016), as well as poor pain and quality of life outcomes (Manzano, Ziegler, & Bennett, 2014). In addition, the patients with higher hospitalization rates shared a belief that pain medicine can harm the immune system (Meghani & Knafl, 2016).

Understanding how patient beliefs inform decisions to use prescribed analgesia is an important aspect of improving pain management strategies and subsequent outcomes (Miaskowski et al., 2001). Researchers have identified distinct patient clusters based on how patients make trade-offs (e.g. type of analgesic, type and severity of side-effects, amount of expected pain relief, and out of pocket costs) in considering analgesic treatment for cancer pain (Meghani & Knafl, 2017). Using choice-based conjoint analysis, these researchers found that a majority of patients may be motivated predominantly by a single salient concern in their decision to use analgesia for cancer pain (Meghani & Knafl, 2017).

We previously found two unique clusters of patients based on how they prioritized their beliefs about analgesic treatment for cancer pain (Rosa, Chittams, Riegel,

Ulrich, & Meghani, 2019). These analgesic treatment belief clusters were identified using a decision-making trade-off methodology known as maximum difference scaling to elicit what beliefs are most important to patients when thinking about analgesic use for cancer pain management. Patients in our study were most likely to trade-off based on the belief that taking pain medicine would keep patients from knowing what is going on in their body (Rosa et al., 2019). A belief that patients who take analgesic for cancer pain become addicted was only moderately important across the sample. (Rosa et al., 2019). Our specific aim for this paper is to assess whether these unique analgesic belief clusters predict objective analgesic use as measured by an electronic medication monitoring system while accounting for relevant confounders.

Methods

Design and Study Population

This study is a secondary analysis of existing data (NIH/NINR RC1-NR011591: PI Meghani, S.H.). The goal of the parent study was to explain racial and ethnic disparities in cancer pain outcomes, specifically to elicit trade-offs that patients with cancer pain employ in making cancer pain treatment decisions (using Choice-based Conjoint analysis) and their actual adherence to scheduled analgesic treatment using electronic monitoring with the Medication Event Monitoring System (MEMS®) (Meghani et al., 2013; Meghani et al., 2015). The parent study used a prospective observational design employing repeated measures at baseline (T1) and 3-month follow-up (T2). Patients were recruited from two outpatient medical oncology clinics of the

University of Pennsylvania Health System in Philadelphia between December 2009 and August 2011. The Institutional Review Board (IRB) of the University of Pennsylvania approved the parent study and all participants provided written informed consent.

The current study was deemed exempt by the University of Pennsylvania Institutional Review Board (IRB) as all protected health information was removed from the dataset prior to study commencement and, therefore, it did not meet the definition of human subjects research. Consistent with the parent study, the criteria specified inclusion of patients 18 years of age or older who self-identified as African-American or White, reported a diagnosis of multiple myeloma or solid tumors, endorsed cancer pain, and had been prescribed at least one around-the-clock (ATC) oral analgesic. Patients using transdermal opioid delivery systems, such as fentanyl, were not included in the parent study sample due to MEMS® vial limitations. This current sample includes 207 self-identified African-American and White patients (participant recruitment flow chart from the parent study was previously published (Meghani et al., 2015); a 14% attrition rate was noted between T1 (N=241) and T2 (N=207) with no statistically significant attrition identified by participants' health status or race) (Meghani et al., 2015).

Study Measures

Electronically-Monitored Analgesic Adherence using MEMS®

The MEMS® (MVW Switzerland Ltd., Sion, Switzerland) was employed to measure objective analgesic adherence. MEMS® is a medication bottle cap that uses a microprocessor to record in real time the event and time of a bottle opening. "Dose

adherence" was the primary measure of adherence to ATC analgesics, defined as the percentage of the total number of prescribed doses that were taken by a patient. For instance, if a patient took 80 of 100 prescribed doses during the period of the study, "dose adherence" would be 80%. The procedures for calculating dose adherence were previously described in the parent study (Meghani et al., 2015). Investigators in the parent study performed sensitivity analysis to account for the observer effect (e.g., modified analgesic taking behavior due to awareness of being observed) and compared MEMS® dose adherence from the total number of study days to MEMS® dose adherence if the first 30 days of observation were removed (Meghani et al., 2015). Significant Spearman correlations for all patients in the sample ($P < .001$) suggested strong internal consistency between total dose adherence scores for the study duration and the total dose adherence scores minus the first 30 days of observations. Based on these findings, (Meghani et al., 2015) the MEMS® dose adherence scores measuring all monitored days in the study was selected for use in the final analysis.

Index Analgesic

Around-the-clock analgesics (index medications) were self-reported by patients during the T1 baseline interview and confirmed through a review of electronic medical records. Index analgesics were classified per the WHO's (1986, 1996) analgesic ladder. Categories include step 1 (nonopioids, e.g., nonsteroidal anti-inflammatories such as ibuprofen or acetaminophen), step 2 (weak opioids, e.g., codeine, tramadol), and step 3 (strong opioids, e.g., methadone, oxycodone).

Analgesic Beliefs for Cancer Pain

Maximum difference (MaxDiff) scaling was used to derive patient clusters based on beliefs about analgesic treatment for cancer pain. Cluster membership was originally identified using MaxDiff statistical techniques on JMP® Pro 14 software as previously described (Rosa et al., 2019). MaxDiff is a trade-off methodology rooted in Random Utility Theory (Thurstone, 1927). It permits researchers to elicit increased choice discrimination through forced trade-offs between items and prevents scale use bias by requiring subjects to make clear choices rather than merely rating preference strengths as used in other ranking or discrete choice methods (Louviere, Flynn, & Carson, 2010; Louviere, Flynn, & Marley, 2015; Marley & Flynn, 2015; Sawtooth Software, 2019). MaxDiff data were then subjected to a *k* means cluster analysis. Two unique clusters were identified: cluster 1 (n=53) and cluster 2 (n=154), which correlated with distinct analgesic treatment preferences. Since both clusters shared the same top ranked analgesic belief, cluster 1 was named the "Side effects" cluster and cluster 2 the "Need it later" cluster based on the second highest ranked preference of each group. Additional information on the rationale for the two-cluster model is provided in a previous publication (Rosa et al., 2019).

Self-Reported Barriers to Analgesic Use

The Barriers Questionnaire-II (BQ-II) (Ward et al., 1993) is a 27-item instrument used at baseline (T1) to assess patient beliefs and concerns about cancer pain management. Eight domains related to pain management concerns comprise the BQ-II: 1)

fear of addiction; 2) fear of tolerance; 3) fear of side-effects; 4) fatalism about cancer pain; 5) desire to be a good patient; 6) fear of distracting healthcare providers from treating cancer; 7) fear of immune system impairment through analgesic use; and 8) concern about analgesic use masking a patient's ability to monitory the physiological symptoms of his or her illness. The BQ-II demonstrates strong internal consistency at .89 (Ward et al., 1993) and measured .86 in this study.

Analgesic Side Effects

The Medication Side-Effects Checklist (MSEC) (Ward, Carlson-Dakes, Hughes, Kwekkeboom, & Donovan, 1998) was used to capture side effects of analgesics at baseline (T1). The MSEC identifies the presence, type, and severity of eight analgesic side effects during the prior week (0-10 scale from no severity to extreme severity). Side effects include constipation, drowsiness, nausea, vomiting, confusion, dry mouth, upset stomach, and itching. The MSEC has excellent internal consistency reliability with Cronbach α of .81 (Ward et al., 1998) and was .79 in this study.

Pain Severity and Pain Impact

Baseline measurement of both pain severity and pain impact were elicited at baseline with the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994). The BPI measures worst, least, and average pain scores over the week prior to assessment, as well as current pain level (0-10 scale from no pain to pain as bad as you can imagine). The BPI has been well-documented in research with cancer patients and demonstrates internal consistency reliability using Cronbach α ranging from .77 to .91 (Anderson et al., 2000; Cleeland et

al., 1994; Cleeland & Ryan, 1994; Meghani & Keane, 2007; Meghani et al., 2015; Rhee et al., 2012; Yeager et al., 2019). In this study, the reliability coefficient was .90.

Pain Management Index

The Pain Management Index (PMI) was calculated for each patient according to the WHO (1986, 1996, 2018) guidelines for cancer pain treatment. The PMI is reflective of the relationship between the most potent analgesic prescribed and the patient's self-reported pain level. The PMI is calculated by taking the most potent prescribed analgesic and subtracting the patient's self-reported pain level (classified using the Brief Pain Inventory as mild, moderate, or severe). Insufficient analgesic prescription strength relative to a patient's self-reported pain level is typically demonstrated by a negative PMI score.

Social Support Questionnaire

A six-item abbreviated version of the 27-item Social Support Questionnaire (Sarason, Levine, Basham, & Sarason, 1983) was used to identify patients' level of social support and satisfaction with perceived support. Patients first identify the individuals in their life who provide social support and then rate the level of satisfaction level they experience with the support.

Demographic and Illness-Related Variables

Demographic data were self-reported and included age, gender, self-identified race, marital status, education level, income, and health insurance type. A number of

variables related to illness were gathered through medical chart review including cancer type and stage, time since cancer diagnosis, past history of depression or substance abuse, and comorbidities used to calculate a Charlson comorbidity score (Charlson, Pompei, Ales, & MacKenzie, 1987).

Statistical Analysis

All analyses for the current study were performed using the Stata/IC 15 platform. Descriptive statistics were generated for relevant sociodemographic and clinical variables. Means and standard deviations are provided for continuous variables and frequencies and percentages for categorical variables.

General linear modeling was the primary statistical method used to achieve the study aim. Prior to building the regression model, bivariate analyses between predictor variables and the outcome adherence variable were assessed. Relevant sociodemographic and clinical variables significant at the bivariate level ($p \leq .20$) at T1 were considered as potential predictors of MEMS® dose adherence at T2. Two models were then constructed.

For model 1, variables that met the $p \leq .20$ criteria, in addition to theoretically salient variables (e.g., history of substance abuse and presence of depression), were used to construct a preliminary prediction model employing a backward elimination method. The backwards elimination method is useful in evaluating the value of each potential predictor when studying a phenomenon that may be influenced by a number of confounders (Cohen & Cohen, 1983). After starting with all individual potential

predictors in the preliminary model, we then subsequently removed any variable that improved the model most significantly by its deletion. This elimination process included theoretical variables. We repeated this process until no additional model improvement was possible and all predictors were significant at the $\alpha = .05$ level.

In model 2, the same theoretically salient variables used in the first model were included. The clusters variable was then entered as a dichotomous categorical variable with cluster 1 and cluster 2 as levels to evaluate the impact of analgesic treatment beliefs on analgesic adherence by observing any change in the R-squared value. The clusters variable was the primary variable of interest and, therefore, was retained in the backward elimination process, regardless of statistical significance. This is consistent with the statistical convention to maintain insignificant findings in a final model when the explanatory variable is of primary interest or there is a specific hypothesis about a given variable (Grace-Martin, 2020; Heinze & Dunkler, 2017).

Variance inflation factors suggested low levels of multicollinearity among predictors in both models one and two (1.49 and 1.43 respectively) (Chatterjee & Yilmaz, 1992). Using studentized residuals during residual analysis, no observations fell beyond the criteria of concern ($x > 3$, $x < -3$). The outcome variable was assessed using histograms and Shapiro-Wilk test (0.87), neither of which showed concerns with violations of normality assumptions. In addition, MEMS® dose adherence was subjected to a sensitivity analysis to remove two observations significantly greater than 100% adherence, which did not change the Shapiro-Wilk value.

Results

Subjects (N=207) had a mean age of 53.8 years (SD=11.1), less than half identified as African-American (41.5%), and most were female (56.5%). The majority rated their general health as “good” (30.4%) or ”fair” (37.2%); less than 5% of the sample rated their general health as “excellent” at baseline. Most patients denied a history of substance abuse (83.1%) or current presence of depression (58%). Table 1 shows subjects by demographic and illness variables for the entire sample and by cluster; no significant differences between clusters were identified. Table 2 shows the belief clusters identified in our prior study (Rosa et al., 2019).

Examining the sample by analgesic and pain management variables (Table 3) shows that patients used a total of roughly 2.1 analgesics to treat their pain, with the vast majority (80.2%) prescribed a strong opioid (WHO step 3). Their average least to worst pain scores over the previous week ranged from 3.4 to 6.9 out of 10 respectively. Clusters 1 and 2 differed significantly in how they rated severity of side effects (p=0.043). There were no statistically relevant differences between clusters in terms of other variables, such as pain management index, pain interference, or the number of self-identified barriers to analgesic use.

MEMS Analgesic Adherence

The clusters variable based on analgesic beliefs was not found to be statistically significant at the bivariate level (p=0.709) but was included in all modeling computation as the primary variable of interest. A number of relevant sociodemographic and clinical

variables met inclusion criteria for linear modeling ($p \leq .20$) (Table 4). Both average and worst pain scores were tested for potential inclusion; the average pain score (p=0.004) was selected due to a higher level of significance.

The first model showed that race, side effects, most potent analgesia prescribed, pain relief with analgesics, and the duration of disease were all significant at the $\alpha \leq .05$ level (Table 5). This analysis was initially generated without the cluster variable to evaluate the relationship between other salient correlates and the MEMS variable in the absence of cluster influence. Variables such as average pain score, history of substance abuse, presence of depression, income, age, pain management index, and insurance type were excluded throughout the elimination process. Approximately 21% of objective analgesic adherence variance using MEMS was explained by the final model ($r^2 = 0.207$).

The clusters variable was entered to Model 2 and, following the backward elimination method, the same variables were identified as statistically significant (Table 6). Although the clusters variable was nonsignificant (p = 0.545), it remained in the model as the primary variable of interest. Similar to the first model, these predictors accounted for 21% of variance observed in the analgesic adherence variable ($r^2 = 0.208$).

Discussion

We sought to determine if unique clusters based on patients analgesic treatment beliefs predicted analgesic adherence behaviors objectively monitored using electronic monitoring. We found that analgesic belief clusters were not statistically associated with adherence in this adjusted analysis. However, other clinically relevant factors such as

race, side effects, most potent analgesia prescribed, pain relief with analgesics, and the duration of disease significantly predicted objective adherence to analgesics for cancer pain. The findings raise important questions about the role of patient beliefs, sociodemographic background, and clinical history in relation to adherence behaviors in the setting of cancer pain.

While analgesic treatment beliefs, preferences, and concerns of patients and families have been previously associated with analgesic use (Liang et al., 2013; Meghani & Knafl, 2017; Meghani et al., 2015; Rhee et al., 2012; Simone et al., 2012), our findings in this study show that beliefs ultimately do not explain patients' objective analgesic taking behaviors. For example, we found that in an adjusted analysis accounting for other confounders, it is the experiential variables (e.g., race, side effects, most potent analgesia prescribed, pain relief with analgesics, duration of disease) that matter most in predicting adherence. These experiential variables have all been substantiated by extant literature as having an impact on adherence behaviors (Manzano et al., 2014; Meghani et al., 2013; Meghani et al., 2014; Meghani & Knafl, 2017; Meghani et al., 2015). These covariates are clinically relevant and appear to be interrelated. For instance, stronger opioids may lead to improved pain relief but may also exacerbate the severity of side effects. Additionally, stronger opioids (e.g. WHO step 3) may also relate to more advanced cancer diagnosis and increased adherence (Meghani et al., 2015; Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2017).

Race was the most significant among the covariates within the model, which supports previous research findings. Studies exploring race related to analgesic adherence

have demonstrated that African-American and White patients differ on the beliefs and concerns most important to them. For instance, past analysis of this current sample shows that African-Americans are most concerned about severity of side-effects, which is positively correlated with increased nonadherence behaviors in this population (Meghani et al., 2013; Meghani & Knafl, 2017; Meghani et al., 2015). White patients in the same sample tended to make trade-offs based on the amount of pain relief afforded by analgesic treatment. African-Americans in previous findings were less likely to be prescribed long-acting WHO step 3 opioids than Whites (Meghani & Knafl, 2017).

Importantly, severity of pain was not included in either model 1 or 2 based on our analytical exclusion criteria but remains clinically significant. More potent analgesia may serve as a proxy for pain severity. In addition, disease duration likely serves as an indirect proxy for pain severity as it may imply more serious pain symptoms requiring higher potency analgesics. Of note, although theoretically salient, history of substance abuse also was not a statistically significant variable in the final regression models. This may be due to the fact that the vast majority of patients in the sample did not endorse a history of prior substance abuse.

There are several limitations of this study. First, the analgesic belief clusters used as the primary variable of interest are not exhaustive of all potential patient beliefs. However, we used a well-substantiated tool for eliciting pain management and analgesic concerns in the cancer pain literature. Future research may aim to elicit additional relevant beliefs as they relate to analgesic use for cancer pain or new concerns garnering salience in the current national context. Second, clusters based on analgesic beliefs were

not statistically significant. Nonetheless our research supports further exploration of the extent to which patient beliefs versus other clinical and sociodemographic variables interact with these beliefs to impact cancer pain outcomes. Third, while a two-cluster model was previously identified (Rosa et al., 2019), there are likely multiple groups of patients that prioritize their beliefs differently. We anticipate the findings of this current study are merely a starting point for identifying how variant patient priorities inform analgesic adherence in patient populations. Fourth, while the age of the data is a concern, the parent study collected data at the peak of the first wave of opioid epidemic. Thus, we expect that the unique longitudinal dataset focusing on patients' analgesic taking in the context of opioid crisis has relevance in the current context. Last, while these findings support previous research findings about predictors of adherence, we cannot generalize beyond this sample.

Implications for Nursing

Nurses should observe for changing trends in opioid prescribing practices as they relate to analgesic adherence behaviors. While certain guidelines specific for cancer pain management continue to recommend opioids based on patients' subjective pain report and a combination of short- and long-acting opioids for optimal pain control (NCCN, 2019; WHO, 2018), the broader national conversation on opioid prescribing is turning toward more modest analgesic treatment focused on short-acting opioid use (Dowell et al., 2016). Our findings, in conjunction with the national opioid epidemic discourse, suggest a needed re-evaluation of interventions geared toward improving adherence for cancer pain. As suggested by this sample and a number of other studies (Meghani &

Bruner, 2013; Meghani et al., 2014; Oldenmenger et al., 2017; Rhee et al., 2012), there are clearly subsets of patients that continue to require around-the-clock analgesic prescription to effectively manage pain. Of concern, previous data highlight that patients are not using analgesics for cancer pain on a scheduled basis. For example, previous findings related to this current sample showed only 69% of patients (n=207) were adherent to WHO step 3 short-acting opioids and roughly 74% were adherent to long-acting opioids (Meghani & Knafl, 2017). Although there have been substantial efforts to tailor education for patients to address analgesic beliefs and barriers, systematic reviews show that these interventions neither improve analgesic adherence nor associated pain outcomes for cancer pain (Bennett, Bagnall, & Jose Closs, 2009; Oldenmenger et al., 2018; Oldenmenger, Sillevis Smitt, van Dooren, Stoter, & van der Rijt, 2009). The evidence suggests that continued focus on evaluating key clinical variables, such as analgesic side-effects and pain report, as well as other sociodemographic and economic factors like race, income, and health literacy may be central to improved outcomes associated with cancer pain (Meghani & Bruner, 2013; S.H. Meghani et al., 2013; Meghani et al., 2014; Meghani & Knafl, 2017; Meghani et al., 2015).

Conclusion

This study shows that patient clusters based on analgesic treatment beliefs do not impact adherence behaviors significantly. However, we found clinical variables that speak to the experience of cancer pain and pain treatment are most relevant to analgesic adherence. Our findings affirm extant literature and support ongoing evaluation to

address, through clinical interventions, the key experiential variables that influence pain outcomes for patients with cancer .

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Table 1. Demographic and Illness Variables for Sample and by Analgesic Treatment Belief Clusters.

Variable	Total (N=207)	Side Effects Cluster (n=53)	Need it Later Cluster (n=154)	P-value*
Age, y, mean (SD)	53.8 (11.1)	54.2 (12.5)	53.7 (10.7)	0.798
Time since cancer diagnosis, mo, mean (SD)	36.7 (35.5)	30.5 (29.4)	38.9 (37.2)	0.138
Charlson Comorbidity Index, mean (SD)	4.3 (2.6)	4.4 (2.3)	4.3 (2.8)	0.725
Health literacy, mean (SD)	13.1 (2.6)	13.3 (2.7)	13.0 (2.6)	0.413
Social support, mean (SD)	3.7 (2.1)	4.1 (2.3)	3.6 (2.0)	0.102
Physical health not good, within past 30 days, mean (SD)	14.7 (10.7)	15.7 (11.3)	14.4 (10.5)	0.439
Mental health not good, within past 30 days, mean (SD)	9.5 (10.7)	8.3 (10.1)	9.9 (10.9)	0.333
General health				0.992
Excellent	9 (4.3)	2 (3.8)	7 (4.5)	
Very good	23 (11.1)	6 (11.3)	17 (11.0)	
Good	63 (30.4)	17 (32.1)	46 (29.9)	
Fair	77 (37.2)	20 (37.7)	57 (37.0)	
Poor	35 (16.9)	8 (15.1)	27 (17.5)	
Gender				0.512
Male	90 (43.5)	21 (39.6)	69 (44.8)	
Female	117 (56.5)	32 (60.4)	85 (55.2)	
Race				0.751
African-American	86 (41.5)	23 (43.4)	63 (40.9)	

White	121 (58.5)	30 (56.6)	91 (59.1)	
Marital status				0.397
Married	110 (53)	25 (47.2)	85 (55.2)	
Separated/divorced/widowed	56 (27)	19 (35.8)	37 (24.0)	
Never married	41 (20)	9 (17.0)	32 (20.8)	
Education				0.922
Elementary	3 (1.5)	1 (1.9)	2 (1.3)	
High School	70 (33.8)	16 (30.2)	54 (35.1)	
College/trade school	101 (48.8)	27 (50.9)	74 (48.1)	
More than college	33 (15.9)	9 (17.0)	24 (15.6)	
Job status				0.934
Full-time outside home	43 (20.8)	11 (20.8)	32 (20.8)	
Part-time outside home	12 (5.8)	4 (7.5)	8 (5.2)	
Full-time at home	4 (1.9)	1 (1.9)	3 (1.9)	
Part-time at home	4 (1.8)	0 (0)	4 (2.6)	
Retired	44 (21.3)	11 (20.8)	33 (21.4)	
Unemployed	25 (12.1)	6 (11.3)	19 (12.3)	
Other	75 (36.2)	20 (37.7)	55 (35.7)	
Income				0.861
< 30,000	73 (35.3)	21 (39.6)	52 (33.8)	
30,000-50,000	36 (17.4)	9 (17.0)	27 (17.5)	
50,000-70,000	37 (17.9)	7 (13.2)	30 (19.5)	
70,000-90,000	24 (11.6)	6 (11.3)	18 (11.7)	
>90,000	37 (17.9)	10 (18.9)	27 (17.5)	

Insurance type				0.731
Private	107 (51.9)	25 (47.2)	82 (53.6)	
Medicare	41 (19.9)	13 (24.5)	28 (18.3)	
Medicaid	27 (13.1)	6 (11.3)	21 (13.7)	
Multiple	25 (12.1)	1 (1.9)	5 (3.3)	
Other	6 (2.9)	8 (15.1)	17 (11.1)	
Cancer type				0.541
Lung	32 (15.5)	9 (17.0)	23 (14.9)	
Breast	38 (18.4)	12 (22.6)	26 (16.9)	
Gastrointestinal	31 (15.0)	9 (17.0)	22 (14.3)	
Genitourinary/reproductive	25 (12.1)	4 (7.5)	21 (13.6)	
Multiple myeloma	34 (16.4)	7 (13.2)	27 (17.5)	
Other solid tumors	47 (22.7)	12 (22.6)	36 (22.7)	
Cancer stage				0.721
I	20 (9.7)	2 (3.8)	11 (7.1)	
II	33 (15.9)	7 (13.2)	17 (11.0)	
III	37 (17.9)	6 (11.3)	25 (16.2)	
IV	64 (30.9)	17 (32.1)	43 (27.9)	
Unknown or unsure	53 (25.6)	21 (39.6)	58 (37.7)	
History of substance abuse				0.659
Yes	35 (16.9)	10 (18.9)	25 (16.2)	
No	172 (83.1)	43 (81.1)	129 (83.8)	
Presence of depression				0.379
Yes	87 (42.0)	25 (47.2)	62 (40.3)	
No	120 (58.0)	28 (52.8)	92 (59.7)	

NOTE: Values are n (%) unless otherwise noted.

*P-values are based on t-tests for continuous variables and χ^2 for categorical variables.Clusters 1 and 2 are based on previous findings as discussed in text.

(See table 2 for additional breakdown of clusters.)

Table 2. Analgesic Treatment Belief Clusters (Rosa et al., 2019).

Side Effects Cluster	Rank Order	Need it Later Cluster
▪ Pain meds keep you from knowing what is going on in your body.	1	▪ Pain meds keep you from knowing what is going on in your body.
▪ It is easier to deal with the pain than the side effects that come from the pain meds.	2	▪ If you use pain medicine now, it won't work when you need it later.
▪ It is important to be strong by not talking about pain.	3	▪ Pain meds weaken the immune system.
▪ Many people with cancer get addicted to pain meds.	4	▪ Many people with cancer get addicted to pain meds.
▪ If you use pain medicine now, it won't work when you need it later.	5	▪ Cancer pain cannot be relieved with medications.
▪ If I talk about pain, people will think I'm a complainer.	6	▪ If doctors have to concentrate on pain they won't focus on treating the cancer.
▪ Pain meds weaken the immune system.	7	▪ It is easier to deal with the pain than the side effects that come from the pain meds.
▪ Cancer pain cannot be relieved		▪ It is important to be strong by not

with medications.	8	talking about pain.
▪ Pain meds make you say or do embarrassing things.	9	▪ If I talk about pain, people will think I'm a complainer.
▪ If doctors have to concentrate on pain they won't focus on treating the cancer.	10	▪ Pain meds make you say or do embarrassing things.

*Beliefs were based on the Barriers-Questionnaire-II (BQ-II) domains (see methods) and were ranked using a maximum differential scaling derived *k* -means cluster analysis.

Table 3. Analgesic and Pain Management Variables.

Variable	Total (N=207)	Side Effects Cluster (n=53)	Need it Later Cluster (n=154)	P-value*
Index analgesic, n (%)				0.534
WHO step 1	19 (9.2)	3 (5.7)	16 (10.4)	
WHO step 2	22 (10.6)	5 (9.4)	17 (11.0)	
WHO step 3	166 (80.2)	45 (85.0)	121 (78.6)	
Pain management index (-2 - +3)	0.5 (1.0)	0.5 (0.8)	0.6 (1.0)	0.687
Worst pain (BPI, 0-10)	6.9 (2.4)	7.1 (2)	6.8 (2.4)	0.265
Least pain (BPI, 0-10)	3.4 (2.0)	3.4 (1.9)	3.4 (2.0)	0.533
Average pain (BPI, 0-10)	4.9 (2.1)	5.0 (2.0)	4.9 (2.1)	0.397
Pain interference (BPI, 0-10)	35.2 (15.9)	36.2 (15.8)	34.9 (16.0)	0.309
Severity of side effects (MSEC, 0-80)	25.2 (15.0)	28.8 (15.6)	24.0 (14.6)	0.043
Barriers Questionnaire (BQ-II, 0-135)	66.8 (20)	63.7 (19.4)	67.8 (20.2)	0.200
Total number of analgesics prescribed (excluding co-analgesics)	2.1 (0.8)	2.2 (1.0)	2.0 (0.7)	0.155
Total number of co-analgesics prescribed	0.2 (0.5)	0.3 (0.6)	0.2 (0.5)	0.322
% overall adherence	65.1 (34.5)	63.6 (33.9)	65.6 (34.9)	0.645

NOTE: Values are mean (SD) unless otherwise noted.

Abbreviations: WHO, World Health Organization; BPI, Brief Pain Inventory; MSEC, Medication Side-Effects Checklist; BQ, Barriers Questionnaire

*P-values are based on t-tests for continuous variables and χ^2 for categorical variables.

Clusters 1 and 2 are based on previous findings cited earlier.

Table 4. Bivariate Results of Predictors of MEMS® Adherence Included in Linear Modeling.

Variable	P Value*
Clusters	0.709
Age	0.201
Race	0.000
Income	0.064
Private insurance (missing data n=203)	0.003
Duration of disease	0.010
Side effects magnitude	0.140
Average pain (last week)	0.004
Most potent analgesic	0.002
Pain management index	0.001
Pain relief with analgesics	0.003
Presence of depression	0.329
History of substance abuse	0.260

*P-values are based on bivariate analysis of variance (ANOVA) for all variables.

Table 5. Predictors of Objective Analgesic Adherence Excluding Clusters Variable.

Variable	F Statistic	P-Value*
Race	19.27	0.000
Side effects	4.22	0.041
Most potent analgesia	3.45	0.034
Pain relief with analgesics	7.69	0.006
Duration of disease	9.05	0.003

*P-values based on general linear modeling.

**r^2=0.207

Table 6. Predictors of Objective Analgesic Adherence Including Clusters Variable.

Variable	F Statistic	P-Value*
Clusters	0.37	0.545
Race	19.27	0.000
Side effects	4.22	0.041
Most potent analgesia	3.45	0.034
Pain relief with analgesics	7.69	0.006
Duration of disease	9.05	0.003

*P-values based on general linear modeling.

**r^2=0.208

CHAPTER 5

Summary of Integrated Findings and Discussion

Summary of Integrated Findings and Discussion

Through literature review, conceptual and empirical analyses, and iterative syntheses of findings, this dissertation explored patients' analgesic treatment beliefs for cancer pain and the association of those beliefs with objective analgesic adherence behaviors. This timely focus is critical to better understanding how patient beliefs, analgesic adherence measures, and cancer pain management intersect in the context of the opioid epidemic. Importantly, the significance of this work is rooted in the high prevalence of moderate to severe cancer pain (Shi et al., 2011; van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016), as well as the policy and scientific initiatives that are impacting opioid monitoring and prescribing practices, as well as pain relief guidelines across settings (Christie et al., 2017; National Academies of Sciences, 2017, 2018; National Academy of Medicine, 2017; U.S. Department of Health and Human Services, 2019).

Despite cancer pain guidelines that identify World Health Organization (WHO) step 3 opioids (e.g., morphine, hydromorphone) as the foundation of moderate to severe cancer pain treatment plans (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; WHO, 2018), other recommendations discourage the use of such opioids for cancer survivors or patients not receiving palliative or end-of-life care (Dowell, Haegerich, & Chou, 2016). Discrepancies in these guidelines have contributed to oncology clinicians' uncertainty about opioid prescribing and use, as well as potential risks to patient safety given differing expert recommendations (Meghani & Vapiwala, 2018; Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2018). The interplay of

divergent pain management guidelines, high cancer pain burdens, and the clinical implications of the opioid epidemic - such as pre-authorization insurance requirements for analgesics and more conservative prescribing practices – require more research that elucidates the factors influencing patients' analgesic taking behaviors (Johnson et al., 2018; Lamar, 2018; National Academies of Sciences, 2017).

There has been much described throughout the prior chapters about the prescriber and healthcare system aspects of analgesic use. However, there continues to be an empirical gap in understanding patients' beliefs about analgesic treatments for cancer pain, and especially, how those beliefs inform their objective analgesic adherence. Three studies were conducted to achieve the overall aim. The first was a concept analysis (chapter 2) that provided a basis for later data analyses and a lens through which to consider study findings. Subsequently, in chapters 3 and 4, we quantitatively explored the phenomenon of interest by analyzing the significance of patients' cancer pain treatment beliefs and then determining the correlation of those beliefs with their analgesic adherence behaviors. The purpose of this chapter is to articulate overall conclusions through a review of chapter aims and synthesis of key findings, implications for future practice, education, research, and policy domains, and the major strengths and limitations of the dissertation.

Review of Chapter Aims and Synthesis of Key Findings

In chapter 1, we provided an overview and background of the phenomenon of analgesic nonadherence, particularly in the context of the opioid epidemic. Additionally,

we made explicit the innovation of this current work and identified the relevant sample and variables from the parent study, as well as the methods, to be used throughout the dissertation. In this first section, the salience of additional scientific inquiry pertaining to analgesic adherence for cancer pain was emphasized, including a substantive literature gap and critical need to better understand the patient perspective related to analgesic use for cancer pain.

In chapter 2 (Rosa, Riegel, Ulrich, & Meghani, 2020), a concept analysis of analgesic nonadherence for cancer pain in a time of opioid crisis using the Walker and Avant (2019) method was presented. The purpose was to clarify the concept of analgesic nonadherence for cancer pain and qualify its utility in the context of the epidemic. To our knowledge, this was the first conceptual analysis of analgesic nonadherence among this population and was a vital step to clarifying how the concept is employed and measured in the literature, and the impact of differing analgesic adherence behaviors on patients and cancer pain outcomes.

Of note, we found that few studies made the link between analgesic nonadherence and patient outcomes. For example, only one study identified inconsistent opioid adherence for cancer pain as the strongest predictor of hospitalization (Meghani & Knafl, 2016). In addition, increased nonadherence due to patient or family hesitancy to use analgesics as prescribed was correlated with increased pain severity and negative consequences on physical and social function that decreased overall quality of life (Lee et al., 2015; Manzano, Ziegler, & Bennett, 2014). In fact, the lack of empirical data alongside the widespread implications of the opioid crisis and dissonance among pain

management guidelines created a lack of clarity about the utility of analgesic nonadherence as a concept in the field.

Ultimately, the concept analysis provided a rationale for the additional studies in chapters 3 and 4. The synthesis of the literature created more questions than answers. First, the specific elements that constituted optimal adherence behaviors related to prescribed analgesics for cancer pain were unclear. Both a lack of evidence in conjunction with the practice and policy changes discussed above made evident the need for additional empirical findings that elucidated the phenomenon of analgesic nonadherence for the cancer patient population. Second, although the national sociopolitical dialogue has focused on how to balance social welfare with individual pain alleviation in this time of opioid crisis (National Academies of Sciences, 2017), more data was needed to better understand what factors influence patients' adherence behaviors. Third, the disagreement between opioid prescribing guidelines, as well as the lack of empirical evidence to support those guidelines, is a barrier to understanding analgesic nonadherence for cancer pain. For example, as argued by Meghani & Vapiwala (2018), the Center for Disease Control (CDC) guidelines discourage the concomitant use of extended- and immediate-release opioids (Dowell et al., 2016) while a number of national organizations promote this multimodal approach for effective pain relief (NCCN, 2019; Paice et al., 2016; WHO, 2018). Analgesic nonadherence in this time of the CDC guidelines – and in the absence of high-quality empirical data to support these guidelines - complicates clarity around prescribing, monitoring, and effectiveness. Fourth, many studies used various surveys and instruments to measure adherence rates

but there was a substantial gap related to the underlying patient decision-making processes that inform analgesic taking behaviors. This gave validity to the need to further explore the decision-making utilities employed by patients when thinking about their analgesic medications to treat their cancer pain.

In chapter 3 (Rosa, Chittams, Riegel, Ulrich, & Meghani, 2019), we briefly discussed how many patients with cancer pain deviate from their prescribed analgesic regimens for a host of reasons (e.g., severity of side effects, concern about dependence or addiction, family or caregiver hesitancy to use analgesics), including their analgesic treatment beliefs (Manzano et al., 2014; Meghani & Bruner, 2013; Meghani, Chittams, Hanlon, & Curry, 2013; Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Rhee, Kim, & Kim, 2012; Schumacher et al., 2014b; Simone, Vapiwala, Hampshire, & Metz, 2012). Specifically, the aims of this study were to (1) elicit the trade-offs patients make based on their beliefs about analgesic use; (2) rank utilities (importance scores) using a maximum difference (MaxDiff) scaling-derived *k* means cluster analysis to evaluate how beliefs differed between groups; and (3) describe clusters by comparing key sociodemographic and clinical variables. MaxDiff - a consumer preference tool rooted in random utility theory (Thurstone, 1927) - is underutilized in the social sciences literature and provided us with an innovative empirical approach to understanding how groups of patients prioritize their beliefs around analgesic treatment for cancer pain, based on a widely used barriers to cancer pain management validated instrument (Ward et al., 1993).

A primary finding of chapter 3 was that patients' beliefs are significant in their choices when thinking about pain medicines. This finding aligns with extant literature

showing an association between analgesic beliefs and analgesic adherence behaviors (Liang et al., 2013; Meghani & Bruner, 2013; Torresan et al., 2015; Valeberg, Miaskowski, Paul, & Rustoen, 2016). The analysis showed that trade-offs based on particular beliefs about cancer pain management strongly effected choices about analgesic use.

For instance, patients across the sample were about 24% more likely to make trade-offs about analgesic medications based on the belief that "pain meds keep you from knowing what is going on in your body". In other words, "knowing body" was identified as the most important belief and patients were more likely to make choices based on this belief over other beliefs. In fact, the belief of "knowing body" may be a key aspect of understanding primary concerns regarding analgesic taking behaviors among patients with cancer who experience pain. Researchers have found that many patients link the presence of pain with disease status and, therefore, the need to "know their body" is crucial (Rau et al., 2017). Furthermore, patients who have shown intentionally nonadherent behaviors (e.g., stop taking analgesics when they feel better or worse) agree with the belief of "knowing body" (Meghani & Bruner, 2013). This suggests that the desire to "know body" may often be prioritized over adherence to prescribed analgesic regimens or the need to mitigate pain symptoms. Additional studies show that some patients deny pain as a symptom of disease (Torresan et al., 2015) and others believe opioids should only be used in advanced disease stages (Liang et al., 2013), supporting the idea that analgesics may only be more readily utilized when patients have a reliable understanding of what is happening in their bodies.

Given the urgency surrounding the national opioid epidemic discourse, it was somewhat surprising to see that patients across the sample in our MaxDiff study ranked the belief that "many people with cancer get addicted to meds" as only moderately important (ranked fourth out of ten beliefs). Taking into consideration that these data were collected during the second wave of the opioid crisis in the United States (2009-2011), we originally anticipated that subjects would have given more weight to this belief. Some previous studies do acknowledge patient concern about physiological dependence or addiction to opioids as a decision-making factor affecting analgesic use (Jacobsen et al., 2014; Liang et al., 2013; Simone et al., 2012). However, our findings support previous research that addiction concerns do not ultimately explain either objective or subjective measures of analgesic adherence in the cancer patient population (Meghani et al., 2015; Rhee et al., 2012). If the parent study were to be replicated today, we assume addiction concerns might generate a higher utility given the consequences of the third wave of the epidemic that started in 2013 (CDC, 2018) related to synthetic opioid overdose deaths. This would support other recent findings that show addiction was the second top concern among ambulatory patients undergoing active cancer treatment (Meghani et al., 2020). The MaxDiff trade-off findings highlight the need to better understand how patients' preferences and beliefs related to analgesic use may differ from national research and policy initiatives focused on more conservative opioid prescribing practices to mitigate addiction risk.

Following the initial MaxDiff operation, a cluster analysis identified two distinct clusters of patients based on analgesic treatment beliefs, representing unique decision-

making utilities. A primary takeaway from this analysis shows that there is significant variation in how clusters of patients prioritize their beliefs related to cancer pain treatment, and this variation likely reflects differences in individual beliefs and the utility of those beliefs when thinking about analgesic use. The only sociodemographic or clinical variable that differed significantly by cluster was the belief that "it is easier to deal with the pain than the side effects that come from the pain meds". This outcome aligns with empirical data associating an increased number of side effects and severity of those side effects with an increase in nonadherence to analgesics (Manzano et al., 2014; Meghani & Bruner, 2013; Meghani et al., 2014). Our findings suggest that the utility of the "side effects" belief may be salient concern for some patients with cancer pain and not for others. Thus, it appears that patients prioritize beliefs around analgesic use quite differently. In fact, the cluster analysis showed significant variation between how the two clusters prioritized analgesic treatment beliefs. This variation likely reflects individual belief differences and the weight patients give to those beliefs regarding analgesic use trade-offs. This outcome is consistent with researchers who found more than a quarter of patients traded-off on analgesic decisions based on a number of differing concerns, including the type and the severity of side effects (Meghani & Knafl, 2017).

Subjects in cluster 2 ranked the belief, "If you use pain medicine now, it won't work when you need it later," as the second rated utility. Patients have previously noted concern that if opioids are used in earlier stage disease than their analgesic effect may be less potent later on as symptoms worsen (Liang et al., 2013). This worry about tolerance to pain medication is likely an ongoing concern for patients with moderate to severe

chronic cancer pain who require analgesic treatment over time. Findings show that pain continues to be one of the top three most troubling symptoms at one-year post-diagnosis and cancer survivors tend to report levels of pain similar to those undergoing active treatment (Shi et al., 2011). A number of utility scores were ranked quite low among both clusters, including, "Won't focus on cancer," "Be strong," "Say embarrassing things," and "Complainer." These low-ranking utilities reflect a prior study showing that for patients with cancer pain, these beliefs are less important than "Knowing body" or "Harm immune system" (Valeberg et al., 2016).

The analysis conducted in chapter 4 explored whether the analgesic treatment belief clusters from the previous chapter predicted objective analgesic adherence behaviors using an electronic medication monitoring system known as the Medication Event Monitoring System (MEMS®; MVW Switzerland Ltd., Sion, Switzerland). A general linear modeling was used with a backward elimination approach to identify significant correlates of MEMS® adherence data (Cohen & Cohen, 1983). Relevant confounders and theoretically salient variables were accounted for throughout the analysis to determine the significance of sociodemographic (e.g., race), clinical (e.g., duration of disease), and pain-related (e.g., most potent analgesia prescribed and pain relief with analgesics) explanatory factors.

Prior to conducting the chapter 4 analysis, we hypothesized that analgesic treatment belief clusters would be predictive of objective analgesic adherence. However, they were not statistically significant in our linear modeling results. Chapter 3 findings suggested that analgesic treatment beliefs weigh significantly in the choices patients

articulated regarding analgesic use and there are unique subgroups of patients based on these analgesic beliefs. However, our chapter 4 outcomes showed that beliefs did not predict objective adherence behaviors. In fact, in an adjusted analysis when accounting for relevant confounders, it was ultimately experiential variables that drive their objective analgesic use. For example, multiple predictors of adherence were noted and support findings from prior studies, including race, side effect severity, the type of analgesia prescribed, pain relief from analgesics, and the duration of disease (Manzano et al., 2014; Meghani et al., 2013; Meghani et al., 2014; Meghani & Knafl, 2017; Meghani et al., 2015). These variables explained 21% of the variance in electronically-monitored analgesic adherence at T2.

Among these factors, race was the most significant predictor in the model and has consistently been shown to impact adherence behaviors. Our findings reflect those of other researchers who have shown, for example, that African-Americans are less likely to be prescribed an extended-release WHO step 3 opioid for cancer pain management than Whites and also have increased concern about analgesics side-effect severity, correlating with increased nonadherence behaviors (Meghani & Bruner, 2013; Meghani & Knafl, 2017; Meghani et al., 2015). The remaining covariates are clinically relevant. In Chapter 4 we give the example of how these variables relate to one another and adherence behaviors: Stronger opioids may lead to improved pain relief but may also exacerbate the severity of side effects. Additionally, stronger opioids (e.g. WHO step 3) may also relate to more advanced cancer diagnosis and increased adherence (Meghani et al., 2015; Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2017).

It is important to note the clinical relevance of pain severity in the analgesic adherence and cancer pain research. Although pain severity was not statistically significant in our linear models based on our analytical exclusion criteria, a number of the variables that were predictive of adherence may serve as proxies for pain severity. For instance, more potent analgesia and duration of disease, both of which indirectly imply greater levels of pain and potentially disease progression. In addition, history of substance abuse was not found to be significant in our modeling, however, a majority of subjects in this sample did not report history of substance abuse.

A key question raised in chapter 4 by these findings is: How useful is the concept of analgesic adherence for cancer pain amid evolving prescribing guidelines secondary to the opioid addiction epidemic? As guidelines continue to emphasize the utilization of immediate-release, as-needed analgesics for pain management, further research and scholarly dialogue should address the validity of measuring adherence behaviors. Adherence - as a measure - is only effective for tracking patient consumption of scheduled, extended-release opioids in this clinical scenario. To this end, our overall findings support a need to re-evaluate how we measure and understand analgesic use for this population. The current literature suggests that patients have low to moderate analgesic adherence rates at best and significant variability in using prescribed analgesics (Meghani & Knafl, 2017). Furthermore, several varied patient education interventions (e.g., booklets, video/computer programs, face-to-face instruction) improve pain outcomes only for a small percentage of patients, likely due to their inability to individualize approaches to alter beliefs or concerns (Bennett, Bagnall, & Jose Closs,

2009; Oldenmenger et al., 2018; Oldenmenger, Sillevis Smitt, van Dooren, Stoter, & van der Rijt, 2009). However, there will continue to be a subset of patients who will require around-the-clock analgesics for the relief of moderate or severe pain where adherence measurement would continue to remain clinically relevant (Meghani & Bruner, 2013; Meghani et al., 2014; Oldenmenger et al., 2017; Rhee et al., 2012).

Better understanding self-management approaches of patients with cancer pain may be integral to improving cancer pain outcomes and understanding underlying analgesic taking behaviors. Of note, researchers have found there are potentially unsafe self-management strategies employed by cancer pain patients that require timely attention, such as self-tapering opioids, cutting pills, substituting extended-release opioids for "as needed" relief, and using over-the-counter and illicit drugs to mitigate or avoid opioids (Meghani et al., 2020). Ultimately, the findings in chapter 4 support continuing to evaluate key structural and clinical variables, such as analgesic side-effects, pain reports, and other sociodemographic and economic factors, such as race, is likely central to improving cancer pain outcomes (Meghani & Bruner, 2013; Meghani et al., 2013; Meghani et al., 2014; Meghani & Knafl, 2017; Meghani et al., 2015; Yeager et al., 2019). Considering analgesic adherence from a broader perspective, integrating beliefs, self-management practices, clinically relevant confounders, and the experiential variables we identified as significant is likely to improve pain outcomes and provide a more in-depth understanding of this phenomenon in the cancer pain setting.

Implications

There are limited empirical data on long-term opioid use (e.g., more than three months) to inform best practices, leading to conflicting opioid prescribing recommendations among guidelines (Dowell et al., 2016; Meghani & Vapiwala, 2018; NCCN, 2019; Paice et al., 2016; WHO, 2018). This has led to concerns about how to best prescribe opioids and other analgesics for cancer pain (e.g., immediate- vs. extended-release, around-the-clock vs. as needed). One of the most relevant questions to emerge from this work is: What is the role of opioid 'adherence' in the era of the CDC guidelines (Dowell et al., 2016) and national concerns with opioid crisis?

Organizational and policy responses are underway to address some of the challenges secondary to the rapid and, at times, misappropriated uptake of the CDC guidelines (Dowell, Haegerich, & Chou, 2019), such as sudden discontinuation or taper of analgesic dosing or barriers to multimodal pain care access. Continued education for prescribers and policy makers that reflects the accuracy of the CDC prescribing guidelines in their entirety is imperative to ensure responsible opioid dosing and planning (Kroenke et al., 2019). When considering the findings from this dissertation amid the opioid crisis, we must evaluate the resources and energy being used to advance the science of analgesic adherence for cancer pain given the evolution of the concept in keeping with many prescribing guidelines (as discussed above). Extant studies already suggest that significant portions of patient samples demonstrate low adherence rates to their prescribed regimens on a scheduled basis (Meghani & Bruner, 2013; Meghani &

Knafl, 2017; Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2017). Therefore, we must consider potential implications across clinical practice, education, research, and policy to promote safe patient outcomes and further understanding the correlates of prescribed analgesic taking behaviors.

Clinical Practice and Education

There are several potential clinical practice and education implications suggested by the findings. First, clinicians might consider exploring and understanding patients' analgesic beliefs throughout the initiation and evaluation of cancer pain treatment plans. Although belief clusters did not correlate with adherence outcomes in our study, patient beliefs were still significant for patients in thinking about their pain medicines according to our MaxDiff utility analysis. Importantly, clinicians should assess for details regarding the *experiences* of cancer pain and pain treatment that inform analgesic beliefs and preferences. Clinicians who both prescribe and administer analgesics may develop plans for eliciting and considering these experiences in relation to prescribed analgesic treatments to better adjust for individual needs. Developing analgesic regimens in partnership with patients amid conflicting pain management guidelines provides an opportunity to promote patient- and family-centered care. Furthermore, a deeper understanding of the patient perspective may improve clinician-patient relationships and more transparent dialogue regarding the status of pain and its effective management.

Second, prescribers must gain a better understanding of what patients believe about the strength of opioids being used. While it has been noted that nonopioids and

weak opioids cause fewer side effects and should be optimized when possible (WHO, 1986, 1996), strong opioids continue to be the recommendation of many guidelines for moderate to severe cancer pain (NCCN, 2019; Paice et al., 2016; WHO, 2018). Understanding potential hesitancies to use opioids from patients and family caregivers will likely assist in ensuring pragmatic interventions for pain relief that are acceptable to the context of the family and caregiver dynamics.

Third, patient-based education programs for patients intended to improve pain-related outcomes have been largely unsuccessful (Oldenmenger et al., 2018). Rather than relying solely on education approaches that are still quite heterogenous (e.g., booklets, video/computer programs, face-to-face contact), a more dexterous investigation of patients' self-management strategies will aid in identifying problematic analgesic taking behaviors and the role of these behaviors on outcomes (Meghani et al., 2019). In addition, further attention to systemic, structural, and sociodemographic factors likely influencing analgesic use, as noted by findings from chapter 4 above, is vital. In fact, improved focus on mitigating side-effects and addressing sociodemographic issues of race, income, and health literacy at the structural and systemic level may have more influence in improving cancer pain outcomes. Considering these confounders during patients interviews and other encounters may facilitate the identification of additional barriers, facilitators, and factors impacting the patient experience of pain, as well as pain relief.

Research and Policy

First, healthcare workers and advocates must continue to support efforts in research and policy that balance societal welfare with individualized pain management (Christie et al., 2017; National Academies of Sciences, 2017, 2018). The dissertation findings suggest that clinicians must continue to better understand individual beliefs and preferences related to analgesic use. At the same time, we must also be cognizant of the impacts of the opioid epidemic on the broader population. This is both a delicate balance and empirical imperative. In particular, the long-term risks and benefits of analgesic use are necessary to explore to ensure an informed patient and clinician population. The high prevalence of cancer pain carries an ethical obligation that pain and its associated suffering be adequately managed through appropriate care planning and pain burden interventions.

Second, additional qualitative research that provides more subjective data on analgesic beliefs and preferences in a time of the opioid epidemic is warranted. While there are a number of qualitative studies available that study the phenomenon of analgesic adherence for cancer pain (Manzano et al., 2014; Schumacher et al., 2014a, 2014b), they largely rely on semi-structured interviews. One recent study utilized a freelisting method, in addition to interviews, to investigate opioid self-management practices for cancer pain patients (Meghani et al., 2020). Methodologies such as concept mapping and ethnographic observation (to the extent possible) may provide additional insights into the behaviors and contextual dynamics surrounding prescribed analgesic taking habits. In particular, approaches that further elicit analgesic beliefs and preferences

from different groups based on the experiences of cancer pain and analgesic treatment options of patients, families, and prescribers may be helpful in understanding divergent priorities among populations. Additional qualitative inquiry may also shed more light on patient concerns not measured in this dissertation and provide further information on how beliefs interact with systemic/structural and family dynamics to influence analgesic taking behaviors and cancer pain outcomes - multifactorial interactions discussed only minimally in prior literature (Schumacher et al., 2014a, 2014b).

Third, further research that explores complementary and integrative health approaches to cancer pain management is needed (Bao et al., 2014). Such interventions are supported by pain management guidelines (Dowell et al., 2016; NCCN, 2019). However, at this time there is insufficient evidence to support their clinical efficacy in managing various types of cancer pain (Hetkamp et al., 2019; Kim, Loring, & Kwekkeboom, 2018; Kim, Kang, & Lee, 2018; Shin et al., 2016; Wayne et al., 2018). As pain outcomes data related to complementary and integrative health services are obtained through expanded research initiatives, policies that increase access to, and plan coverage and affordability of these services - in conjunction with more traditional analgesic and interventional pain relief options - will be imperative to ensure pain care equity across patient populations (U.S. Department of Health and Human Services, 2019).

Finally, continued efforts to clarify the association between patients' analgesic beliefs and analgesic taking behaviors is needed to further personalize care and improve safety and health outcomes. While the two analgesic treatment belief clusters were not statistically associated with objective adherence behaviors in this dissertation work, there

are likely multiple groups of patients that prioritize beliefs in different and nuanced ways, which informs their analgesic use accordingly. Further scientific inquiry should assess for these additional decision-making patterns. In the end, policies that ensure timely pain management for any patient experiencing pain secondary to cancer are needed across institutional and system-wide settings.

Strengths and Limitations

There are a number of strengths of this dissertation. First, a distinct advantage was the use of a rare existing dataset that permitted the measurement of longitudinal and objective analgesic and opioid adherence behaviors in the outpatient oncology setting (Meghani et al., 2015; Meghani & Knafl, 2017). To our knowledge, this is the only dataset that accomplishes these empirics in the United States, with the exception of a single recent study that observed a significantly smaller sample (N=17) (Wright et al., 2019). Second, the sample used was roughly 42% African-American, representing the beliefs, demographics, and pain background of an historically underrepresented group. Third, the final sample used (N=207) was from T2 and showed no disproportionate attrition based on sociodemographic or clinical data from baseline. Last, this dissertation is the first to employ MaxDiff analysis in this particular field, making a strong case for future use of this approach in healthcare research, particularly in order to better understand how patients trade-off on their decision-making processes around analgesic use.

A primary limitation of the empirical portions of the dissertation is the age of the data, which was collected between 2009 and 2011. However, it is important to consider that this time period aligned with the second wave of the opioid crisis, carrying current implications for the ongoing sociopolitical context (CDC, 2018). Second, the sample itself was limited to African-American and White patients, excluding the decision-making utilities of patients from other diverse and minority backgrounds. However, this sample met the aims of the parent study, which focused on cancer pain disparities, specifically between African-American and White patients. Third, while the beliefs evaluated in the MaxDiff questionnaire were based on a well-validated cancer pain barriers tool (Ward et al., 1993), this instrument is likely not inclusive of all potentially influential beliefs considered when trading-off on decisions regarding analgesic use for cancer pain. In addition, while we focused on patient beliefs, the study was not inclusive of provider-, family-, or system-level influences associated with analgesic adherence behaviors or how those factors may impact patients' individual beliefs. Further research is needed to evaluate a more holistic assessment of beliefs and their association with analgesic adherence in the context of these broader interpersonal and structural considerations. To date, there are limited data that explore the impact of family and caregiver hesitancy on analgesic use as discussed above. Lastly, while our findings are confirmatory of previous research findings in this area, we cannot generalize beyond this sample.

Conclusion

Cancer pain is a debilitating and highly prevalent symptom that impacts patients and their families. Analgesics are the cornerstone of cancer pain management and, in particular, opioids continue to be foundational for moderate to severe cancer pain treatment according to cancer pain guidelines. The phenomenon of analgesic nonadherence for cancer pain requires further scholarly dialogue amid this context of the opioid crisis but also additional empirical and normative research to elicit its link to and validity in improving cancer pain and health outcomes.

Our findings suggest that experiential variables rather than analgesic beliefs were associated with analgesic adherence in this sample of cancer outpatients. However, the field needs more investigation to understand exactly how patients prioritize those beliefs in a broader sense, how they trade-off on what is most important to their sense of health and well-being, and how the current climate of the opioid crisis, as well as the input of family and prescribers, influence those beliefs. Importantly, our research supports continued emphasis on systemic and structural influences to understand analgesic taking behaviors - such as race, income, and health literacy - as well as further studies that describe self-management practices related to prescribed analgesics and opioids. These factors must be addressed to ensure pain management equity for all those suffering from cancer pain.

Early in the dissertation, we noted that it is impossible to sever the complexities of the opioid epidemic from the phenomenon of analgesic nonadherence for cancer pain. The opioid epidemic is, indeed, an antecedent of analgesic use for cancer pain. This sociopolitical milieu of the evolving opioid crisis is expected to continually shape patients' beliefs, preferences, and values and health providers' prescribing practices, as well as policies that inform opioid access. Future studies should focus on these multi-level factors and complexities in meaningfully addressing the burden of cancer pain amid the opioid crisis.

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